BMJ Open

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014813
Article Type:	Protocol
Date Submitted by the Author:	21-Oct-2016
Complete List of Authors:	Heazell, Alexander; University of Manchester, Maternal and Fetal Health Research Centre Weir, Christopher; University of Edinburgh, MRC Hub for Trials Methodology Research; Edinburgh Clinical Trials Unit Stock, Sarah; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health,; School of Women's and Infants' Health, University of Western Australia, Crawley WA 6009. (FMM) Calderwood, Catherine; The Scottish Government St Andrew's House, EH1 3DG., Chief Medical Officer for Scotland, CunninghamBurley, Sarah; University of Edinbrugh, Public Health Sciences Froen, Frederik; Nasjonalt folkehelseinstitutt, Division of Epidemiology Geary, Michael; Rotunda Hospital, Parnell Square Hunter, Alyson; Royal Maternity Hospital, Grosvenor Road, BT12 6BB McAuliffe, Fionnuala; University College Dublin, Murdoch, Edile; Royal Infirmary of Edinburgh, NHS Lothian, EH16 4SA., Department of Neonatology Rodriguez, Aryelly; University of Edinburgh, (ECTU) Edinburgh Clinical Trials Unit Ross-Davie, Mary; NHS Education for Scotland, 3rd Floor, Hanover Buildings, 66 Rose Street, EH2 2NN. Scott, Janet; Sands, Victoria Charity Centre, Suite GF2 Ground Floor, 11 Belgrave Road, SW1V 1RB. Whyte, Sonia; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health, Norman, Jane; , Queen's Medical Research Institute, EH16 4TJ
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Research methods
Keywords:	Reduced Fetal Movements, Perinatal Mortality, Stillbirth, Neonatal Death, Fetal Growth Restriction

Study Protocol

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

Alexander E P HEAZELL,[1,2] alexander.heazell@manchester.ac.uk

Christopher J WEIR, [3,4] christopher.weir@ed.ac.uk

Sarah J E STOCK,[5 6] sarah.stock@ed.ac.uk

Catherine J CALDERWOOD,[7] catherine.calderwood@scotland.gsi.gov.uk

Sarah CUNNINGHAM-BURLEY,[4] sarah.c.burley@ed.ac.uk

J Frederik FROEN,[8] frederik.froen@fhi.no

Michael GEARY,[9] mppgeary@gmail.com

Alyson HUNTER,[10] alyson.hunter@belfasttrust.hscni.net

Fionnuala M MCAULIFFE,[11] fionnuala.mcauliffe@ucd.ie

Edile MURDOCH,[12] edile.murdoch@nhslothian.scot.nhs.uk

Aryelly RODRIGUEZ,[3,4] aryelly.rodriguez@ed.ac.uk

Mary ROSS-DAVIE,[13] mary.ross-davie@nes.scot.nhs.uk

Janet SCOTT [14] janet.scott@uk-sands.org

Sonia WHYTE [5] sonia.whyte@ed.ac.uk

Jane E NORMAN.[5] jane.norman@ed.ac.uk

1. Maternal and Fetal Health Research Centre, Institute of Human Development, University of Manchester. 2. St. Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, M13 9WL. 3. Edinburgh Clinical Trials Unit, Edinburgh, UK 4. Centre for

Population Health Sciences, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG. 5. Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health, Queen's Medical Research Institute, Edinburgh, EH16 4TJ.6. School of Women's and Infants' Health, University of Western Australia, Crawley WA 6009. (FMM) 7. Chief Medical Officer for Scotland, The Scottish Government St Andrew's House Edinburgh EH1 3DG. 8. Department of International Public Health, Norwegian Institute of Public Health, PB 4404 Nydalen, N-0403 Oslo, Norway, 9. Rotunda Hospital, Parnell Square, Dublin 1, Ireland. 10. Centre for Fetal Medicine, Royal Maternity Hospital, Grosvenor Road, Belfast, BT12 6BB 11. UCD Obstetrics & Gynaecology, School of Medicine, University College Dublin, Ireland. National Maternity Hospital, Dublin, Ireland. 12. Department of Neonatology, Royal Infirmary of Edinburgh, NHS Lothian, Edinburgh, EH16 4SA. 13. NHS Education for Scotland, 3rd Floor, Hanover Buildings, 66 Rose Street, Edinburgh EH2 2NN. 14. Sands, Victoria Charity Centre, Suite GF2 Ground Floor, 11 Belgrave Road, London, SW1V 1RB.

Abstract

Background - In 2013, the stillbirth rate in the UK was 4.2 per 1,000 live births, ranking 24th out of 49 high-income countries, with an annual rate of reduction of only 1.4% per year. The majority of stillbirths occur in normally formed infants, with (retrospective) evidence of placental insufficiency the commonest clinical finding. Maternal perception of reduced fetal movements (RFM) is associated with placental insufficiency and increased risk of subsequent stillbirth.

This study will test the hypothesis that the introduction of a package of care to increase women's awareness of the need for prompt reporting of RFM and standardised management to identify fetal compromise with timely delivery in confirmed cases, will reduce the rate of stillbirth. Following the introduction of a similar intervention in Norway the odds of stillbirth fell by 30%, but the efficacy of this intervention (and possible adverse effects and implications for service delivery) have not been tested in a randomised trial.

Methods - We describe a stepped wedge cluster trial design, in which participating hospitals in the UK and Ireland will be randomized to the timing of introduction of the care package. Outcomes (including the primary outcome of stillbirth) will be derived from detailed routinely collected maternity data, allowing us to robustly test our hypothesis. The degree of implementation of the intervention will be assessed in each site. A nested qualitative study will examine the acceptability of the intervention to patients and health care providers and identify process issues including barriers to implementation.

Discussion - The data provided by this study will inform the management of women with RFM; which has been recurrently identified as suboptimal in cases of stillbirth. This will provide robust evidence to determine whether increased maternal awareness of RFM combined with a standardised management protocol to identify acute or chronic fetal compromise can reduce stillbirth.

Trial Registration

www.clinicaltrials.gov NCT01777022

Version

Protocol Version 4.1, 18th October 2016

Keywords

Reduced Fetal Movements; Perinatal Mortality; Stillbirth; Neonatal Death; Fetal Growth Restriction.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This trial directly addresses the need for studies of the information given to women regarding fetal movements and the subsequent management of reduced fetal movements identified by Confidential Enquiries into Antepartum Stillbirths, Systematic Reviews and the Stillbirth Priority Setting Partnership.
- A stepped-wedge cluster trial design in combination with routinely collected maternity data allows the trial to be adequately powered to detect a difference in stillbirth as a primary outcome.
- The pragmatic nature of the study represents the potential impact of the introduction of such standardised care into clinical practice.
- The nested qualitative study will provide information regarding the acceptability of the intervention and identify barriers and facilitators to its adoption.
- The lack of information on resource use before and throughout the study period limits the ability to understand the consequences of the intervention on maternity unit workload.

INTRODUCTION

Stillbirth

Stillbirth, defined in the UK as a baby with no signs of life after 24 weeks of completed pregnancy [1], remains the major cause of perinatal mortality in high-income environments, with a recent series of papers in the Lancet on stillbirth issue calling for renewed action in this area [2]. There is no single "cause" of stillbirth, and a significant proportion of stillbirths remain unexplained, but fetal growth restriction, maternal hypertension and low socioeconomic status are amongst the identifiable risk factors [3]. The concept that more can be done to reduce stillbirth in the UK and Ireland is supported by data showing a marked variation in rates between resource rich countries, when similar definitions of stillbirth are used [2]. Notably, the UK has a higher rate than comparable resource rich countries such as Germany, Netherlands, New Zealand and Norway with rates in the UK some 50% greater than those of the Netherlands. Disappointingly, the annual rate of reduction in stillbirth from 2000 to 2014 in the UK was only 1.4% compared to 6.8% in the Netherlands and 2.8% in New Zealand [2]. Rates of stillbirth in Scotland (3.7 per 1,000 births in 2014) and Ireland, at (4.4 per 1,000 livebirths in 2013) are similar to rates in England and Wales at 4.2 per 1,000 livebirths (England and Wales, 2014) [4]. The reduction of avoidable harm for women and babies is viewed as a major priority for Government and its agencies throughout the UK and Ireland. Consequently, several initiatives have been developed by national governments in the UK and Ireland including the Scottish Government Stillbirth Working Group, NHS England Saving Babies' Lives Care Bundle and the Welsh Assembly 1000 Lives Plus strategy. These strategies have identified the need for better evidence to guide efforts to prevent stillbirths.

Using a robust priority setting strategy [5] the Lancet Stillbirth's series steering committee identified issues around detection and management of reduced fetal movements (RFM) amongst the top ten key research questions on prevention and

management of stillbirth [6]. This was confirmed in the UK-based Stillbirth Priority Setting partnership involving over 1,700 parents and professionals which identified two relevant issues among the highest ranked research questions regarding stillbirth: i) which investigations identify a fetus at risk of stillbirth after a mother believes she has experienced reduced fetal movements? and ii) would more accessible evidence-based information on signs and symptoms of stillbirth risk, designed to empower women to raise concerns with healthcare professionals, reduce the incidence of stillbirth? [7] Thus, RFM has been identified as a highly-relevant area of study by parents, professionals and researchers.

Reduced Fetal Movements, Stillbirth and Placental Insufficiency

There is a clear association between maternal perception of RFM and late stillbirth dating back over four decades [8]. In a recent series of 2,000 women, the adjusted OR (95% CI) of late stillbirth in women with RFM (compared with controls) was 2.37 (1.29-4.35) [9]. One international study of 1,714 women who experienced a stillbirth found that 30% had noted significant RFM prior to the diagnosis of stillbirth [10]. Although the mechanisms have not been fully delineated, it is likely that RFM and stillbirth are linked by a common pathology, that of placental dysfunction [11]. There is good evidence linking placental dysfunction and RFM. Women who have fewer fetal movements on ultrasound immediately prior to caesarean section are more likely to have umbilical cord gas measurements indicative of acidaemia, hypoxaemia, and hypercapnia, compared with controls [12]. Women delivering within one week of an episode of RFM show differences in placental structure and function which are reminiscent of those seen in fetal growth restriction (FGR) and stillbirth [13]. Additionally, the odds of fetal growth restriction (FGR, defined as being at less than the 10th centile for gestation adjusted birthweight) were greater in women with RFM compared with controls (adjusted OR 1.6, 95% CI 1.1–2.2 [14]). Taken together these

data are strong evidence that placental dysfunction is associated with RFM, and a causative pathway seems likely.

The evidence linking placental dysfunction and stillbirth is even stronger; a systematic review of placental pathology in stillbirths described abnormalities in up to 65% of cases [15]. Amongst the 291 stillbirths in Scotland in 2010, 137 (47%) had evidence of placental dysfunction [16]. Given that the placenta was examined in only 80% of stillbirths, the true prevalence of placental dysfunction is likely to be higher. In addition, between 20%-40% of stillborn babies are reported to have FGR, as defined by a birthweight less than the 10th centile [17]. Additionally, the Lancet report notes that "placental pathologies accounted for one in four deaths across all gestational ages, and were contributory or causal in more than half of cases" [6]. Given that stillbirth is strongly related to placental dysfunction, and RFM is a "biomarker" of placental dysfunction then better management of women presenting with RFM focussing on the detection of placental dysfunction might reduce the risk of stillbirth.

Formal Fetal Movement Counting

Although prenatal detection of FGR is improved by fetal movement counting [18], a systematic review [19], and a large and influential cluster randomised trial (which dominates the systematic review) showed that routine fetal movement counting using the count to ten charts had no effect on perinatal mortality [20]. Thus, the National Institute for Health and Social Care Excellence (NICE) recommended that "Routine formal fetal movement counting should not be offered" [21]. Importantly, the large cluster randomised trial tested a specific alarm limit for RFM, but did not recommend a specific management strategy for women who did present with RFM. There were two important observations from this study, firstly that in both groups the perinatal mortality rate was lower than contemporary or subsequent periods in the UK and secondly that more women in the fetal movement counting arm came in with a live baby who subsequently died compared with the control arm (19 vs 11), suggesting

that one reason the strategy failed to reduce perinatal mortality was inadequate investigation and management of those presenting with RFM [20].

Efficacy of a package of intervention for RFM

Supportive data for the package of interventions used in this study comes from a large observational "clinical quality improvement study" in Norway which found a significant fall in rates of stillbirth (from 3.0/1,000 to 2.0/1,000 [OR 0.67 95% CI 0.48–0.93]) after the introduction of an intervention package consisting of written information for women about awareness of RFM combined with consensus guidelines for health professionals about their management [22]. Although this study was not randomised, and therefore constitutes only level II-3 evidence, it has informed recommendations from the Royal College of Obstetricians and Gynaecologists (RCOG) and Perinatal Society of Australia and New Zealand (PSANZ) that "women should be advised to be aware of their baby's individual pattern of movements and that if they are concerned about a reduction in or cessation of fetal movements …..they should contact their maternity unit" [23 24].Following initial publication of the Norwegian study, a re-analysis was required as discrepancies between stillbirth rates in the study and the Medical Birth Registry of Norway were identified. This reanalysis found the reduction in stillbirth rates was of borderline statistical significance (OR 0.72, 95% CI 0.50-1.03). The authors concluded that further studies were needed to determine whether this approach was associated with a reduction in stillbirth [25].

Importantly, in the Norwegian study, there was no increase in the proportion of women who presented with RFM when rates were compared before and after the intervention [22]. However, women with RFM presented significantly earlier to hospital than they had hitherto, potentially allowing time for intervention to reduce perinatal mortality. These data suggest that a package of interventions encouraging women with RFM to present early to hospital, combined with a structured approach to their management might reduce rates of stillbirth without contributing to a large increase in

admissions antenatally.

Optimal strategy for determining RFM

There is no uniform threshold of fetal movements below which perinatal morbidity increases [26], and no evidence that a specific threshold performs better than maternal perception of reduced fetal movements alone [8]. Therefore, guidelines from the RCOG and PSANZ [23 24], informed by the Norwegian study [22] suggest that it is maternal *perception* of decreased fetal movement which is important.

Optimal strategy for investigation and management of women presenting with RFM.

A recent systematic review found there are no proven strategies for the investigation and management of women presenting with RFM [27]. Cardiotocography (CTG) is routinely used to ascertain fetal wellbeing, and it is the cornerstone of the RCOG guideline [24]. However, data from Norway, suggests that ultrasound assessment of fetal size is often the most helpful investigation, performing well on both an absolute basis, and compared with other interventions [28]. In a series of over 3,000 women with RFM, ultrasound (including measurement of fetal biometry and liquor volume) was found to be useful in detecting abnormalities in 11.6% of scans. In 71% of women in whom an abnormality was found, ultrasound was the only technique that detected an abnormality. Additionally, 85% of abnormalities detected by ultrasound, were important in informing the clinical management of the woman [28]. These data are supported by a smaller UK study which found that abnormalities detected on CTG or ultrasound scan were most strongly associated with adverse outcome in women with RFM, with identification of abnormal estimated fetal growth centile on scan being the test most highly predictive of poor outcome [29]. Perhaps this is not surprising, given the strong association between RFM and placental dysfunction and the central importance of ultrasound in the identification and management of small for gestational age babies [30]. Given these data, it is concerning that a survey of clinicians in Scotland

showed that fewer than 5% would routinely refer women with RFM for ultrasound examination (unpublished data from June 2012), and a survey of 223 UK midwives and obstetricians described that 17.9% of respondents would perform an ultrasound scan [31]. These views of clinicians may reflect the variable quality of local guidelines, which are frequently not based on national recommendations, even those for which there is strong evidence [32].The variation in information given to women and subsequent management of RFM has been highlighted as sources of suboptimal care in two confidential enquiries into antepartum stillbirth [33 34]. Therefore, we believe that current investigation of women presenting with RFM is inadequate, hence using the best available evidence, we have drafted what we consider to be a robust evaluation protocol for investigation of women with RFM.

Potential harms of a package of care around increased awareness and optimised management of RFM

Any clinical intervention which aims to improve outcomes also has the ability to do harm. Thus, it is essential that the intervention proposed is rigorously evaluated using the gold standard technique of a randomised trial, rather than being introduced as a service development. When the study began, there was a small window of opportunity to do this, as the enthusiasm to improve current management of RFM is such that routine introduction of the package of care is unlikely to be delayed much further than the current scheduled end date of this study. Possible harms of a package of care consisting of a management plan for identification and delivery of the "at risk" fetus, together with strategies for increasing pregnant women's awareness of the need to report early include increased maternal anxiety and increased intervention (including hospital admission, induction of labour and Caesarean section) which itself is associated with pregnancy related complications. The available evidence is reassuring on some of these issues. Encouraging women to be aware of

fetal movement does not increase maternal anxiety [35], and it appears to have a neutral effect on maternal- infant attachment [36]. In the Norwegian service development study, the package of care increased rates of follow up of women, but there was no increase in admissions overall, admissions for induction or admissions for emergency caesarean section [22] – again, whilst reassuring these outcomes require formal evaluation in a randomised and relevant setting to the UK and Republic of Ireland. The final possible harm of the package is around increased resource use, and the opportunity cost of focussing on RFM rather than other potential methods to prevent stillbirth.

RATIONALE

The aim of this study is to test the hypothesis that a package of interventions consisting of strategies for increasing pregnant women's awareness of the need to report early when they perceive a reduction in fetal movements, followed with a management plan for identification and delivery of the "at risk" fetus in such women, will reduce rates of stillbirth.

STUDY OBJECTIVES

Primary Objective

The primary objective is to answer the research question 'Does the introduction of a protocol for detection and management of decreased fetal movements reduce rates of stillbirth?' The secondary objectives are to answer the following research questions:

- What is the effect of the intervention on rates of caesarean section and induction of labour?

- What is the effect of the intervention on rates of admission to the neonatal intensive care unit?
- What is the effect of the intervention on the proportion of women with FGR remaining undelivered by 40 weeks gestation?
- What is the acceptability of such a package of care to pregnant women and their health care providers?
- What other process outcomes are influenced by the intervention, such as health care provider/patient interactions?

ENDPOINTS

Primary Outcome

The primary endpoint is stillbirth (antepartum and intrapartum). We will use the UK definition of stillbirth which is "a baby delivered without signs of life after 23^{+6} weeks" [4]. Where gestation is uncertain we will include all babies with a birth weight of 500g or more.

Secondary Endpoints

Other measures of perinatal mortality including:

- Stillbirth at 28 weeks gestation and above (WHO definition of stillbirth)
- Stillbirth at 22 weeks gestation and above (international stillbirth alliance definition)
- Stillbirths amongst normally formed infants of 22 weeks gestation and above, 24 weeks gestation and above and 28 weeks gestation and above
- Perinatal mortality (defined as stillbirth at 24 weeks gestation and above and deaths in the first seven days of life)
- Rates of caesarean section

- Rates of induction of labour
- Rates of admission to the neonatal intensive care unit (and their reasons)
- Rates of admission to the neonatal intensive care unit for more than 48 hours
- Proportion of infants with fetal growth restriction (less than the 10th centile, customised for gender) remaining undelivered at or after 40 weeks gestation
- Birthweight centile (according to https://www.gestation.net)
- Rates of spontaneous vaginal delivery

We will also collect the following data to allow adjustment for these variables: maternal age, maternity unit of delivery, birthweight, gestation of delivery, parity, gestation, sex, smoking (current and ever), maternal body mass index (BMI), number of babies (one or more), ethnicity (to allow a customised birthweight centile to be generated), method of delivery, deprivation category (where available) and other neonatal variables including Apgar score and encephalopathy.

STUDY DESIGN

This is a multicentre, stepped wedge cluster randomised trial of a package of care consisting of a management plan for identification and delivery of the 'at risk' fetus, together with strategies for increasing pregnant women's awareness of the need to report RFM early. The study will take place in participating hospitals in the UK and Ireland (a complete list is available http://www.crh.ed.ac.uk/affirm/randomised-hospitals/). A nested qualitative study will examine the acceptability of the intervention to patients and health care providers and identify process issues (barriers to implementation). Clinical audit conducted after the change in practice will be used to determine the effect of interventions on process outcomes (e.g. number of women presenting with reduced fetal movements, interval between perceiving

reduced fetal movements and presentation to hospital, number of ultrasound scans, number of admissions for induction of labour). A diagram indicating randomisation of hospital groupings in the stepped wedge design is shown in Figure 1.

The interventions will be introduced over a 33 month period. Data will be collected over a 36 month period. Data in the 'active phase' after introduction of the intervention will be compared to data in the 'control phase' – the period during which usual care processes in study sites are followed from study start to the time of introduction of the intervention. Given that it will take individual units some time (a) to effect change in management in their unit from time of introduction of the intervention and (b) that it will take some time for this change in practice to impact on clinical outcomes, we plan a "washout" period of two months after the introduction of the intervention during which data will not be included in either group for analysis.

STUDY POPULATION

Number of participants

Participants will be those delivering at all the sites over the study period (36 months). All eligible women will be recruited to the cluster randomised controlled trial. Based on previous delivery numbers, after accounting for a washout period of two months (and assuming no withdrawals or losses to follow up) this is estimated to be a total of around 143,140 women per annum. A subset of around 30 participating women and 30 midwives, sonographers and obstetricians will be recruited to the nested qualitative study, which is based in the Scottish sites.

Inclusion criteria

We will include all women delivering at one of the participating maternity units for the duration of the study. Women who have been seen at any of the maternity units but who deliver at home will not be included. The duration of the study will be 42 months

from the start of the trial (01/02/2014). For practical reasons, participants for the nested qualitative study will be recruited from the participating units in Scotland.

Exclusion criteria

We will exclude women as follows:

- Women for whom data on delivery outcomes is still unavailable four months after the date of delivery
- Women delivering in the "washout" period in each unit.

Members of the trial management group and participants who do not speak/understand English will be excluded from participating in the nested qualitative study.

Identifying participants

Women will be identified from those whose data is included in routine data returns from each unit. Potential participants for the nested qualitative study will be identified from those attending antenatal clinics in participating hospitals, and/or local staff.

Consenting participants

The main study is a stepped wedge cluster randomised trial of a package of care which would be introduced in many of the participating units regardless of whether the trial was on-going or not and the trial uses only routinely collected data on participants. The ethics committee indicated that formal individual patient consent is not necessary for the main trial. Participants in the nested qualitative study will be asked for individual consent.

Screening for eligibility

As participants are not directly recruited we will not perform any specific screening tests for this aspect of this project. Participants for the nested qualitative study will be: (i) Pregnant women attending hospitals who are participating in the main trial in

Scotland. Purposive sampling will ensure that the final sample set includes women who have and who have not experienced RFM, both before and after the introduction of the intervention; (ii) Hospital staff (including midwives, ultrasonographers and obstetricians/radiologists) working in participating hospitals in Scotland. There will be no specific screening tests for eligibility for the nested qualitative study, except that women who have experienced a stillbirth in the index pregnancy will not be approached.

Ineligible and non-recruited participants

Potential participants for the nested qualitative study who are not approached or who decline will have no specific interventions / procedures.

Withdrawal of Study Participants

The nature of a cluster randomised study is such that it is not possible for the participant to withdraw from the "cluster" unless she changes maternity unit part way through her pregnancy. We plan to collect routinely recorded anonymised data; patients have the right to opt out of having their data used – if this happens their data would be excluded from the study database (e.g. under the Confidentiality and Security advisory Group Report 2002 and the Data Protection Act (1998) requirements for fair processing of data). Participants in the nested qualitative study who wish to withdraw will be allowed to do so. Their data will be retained and used, unless they additionally indicate that they wish to withdraw their data.

RANDOMISATION

Randomisation Procedures

This is a cluster-randomised, stepped-wedge design trial wherein maternity units rather than individual patients are randomised. All units will implement the fetal movement monitoring intervention at some point during the trial; the random element is the time point at which this will occur, the so-called "step" of the stepped-wedge

design. Participating maternity units will be blinded to their randomly allocated time point until the time this is required to be revealed to enable the necessary training in the implementation of the intervention to be delivered. Primary and secondary outcomes of the trial will be gathered in a blinded manner via routinely collected data sources.

Groups of units which are in close proximity to each other will be treated as strata for the purposes of randomisation. This will assist with the feasibility of delivering the training for and implementation of the intervention. Furthermore, this local synchronisation of the intervention implementation will minimise the chances of contamination (introduction of the intervention prematurely) from maternity units which have already implemented the intervention to those not yet randomised.

The order in which the strata of units step in to implement the intervention will be determined by computer generated random numbers from a uniform distribution. The randomisation list will be held by the Edinburgh Clinical Trials Unit (ECTU). The identities of the research team staff whose roles in the trial require them to be unblinded to randomisation codes will be recorded in the trial master file (TMF).

Treatment Allocation

Participating sites will be randomised to the intervention or conventional clinical management. All units will be providing conventional treatment at baseline according to local practice – this is the treatment established before the study starts. Sites will be randomised to “active” treatment in turn as described above. Active treatment will consist of a package of care consisting of a management plan for identification and delivery of the ‘at risk’ fetus, together with strategies for increasing pregnant women’s awareness of the need to report RFM early. The recommended management plan for identification and delivery of the “at risk” fetus is shown in Figure 2. Practice change in the active units will be achieved by: (i) written/email information to all clinicians (doctors, midwives and ultrasonographers) in each unit about the study protocol and

amendment of the local protocol for Reduced Fetal Movements (RFM) to that of the study protocol; (ii) a short web-based training package taking approximately one hour to complete for all clinicians in each centre and (iii) training /information sessions to run in each unit and (iv) posters in each unit to describe the practice change. Strategies for encouraging clinicians to increase pregnant women's awareness of fetal movement will include all the above and also a fetal movement leaflet for pregnant women (shown in Supplementary Information 1). Once units have begun active treatment it is not anticipated that they will return to conventional treatment. We will conduct an audit of women presenting with reduced fetal movements and assess the proportion of staff completing the online training to assess the extent to which sites have followed the intervention plan.

Units will be informed about treatment allocation as near as possible to the implementation of the "active" treatment. For practical purposes, we anticipate that each unit will need around three months' notice before the "active" treatment is introduced, hence units will be informed of the timing of their treatment allocation (step) three months before the active treatment is due to start. The treatment allocation will not be administered blind and there are no restrictions on concomitant care or other interventions during the study, hence there is no need for emergency unblinding and there are no stopping rules for the study.

DATA COLLECTION

For the main trial, data will be accessed from the information routinely collected during the clinical management of the patient. For consistency, we will normally only include data items which become available within four months after the delivery date in question, although we may seek advice from the independently-chaired trial steering committee (TSC) about exceptions as they arise. Different data sources will be used for different regions of the study: (i) In Scotland the source data will be SMR2 and the Scottish Birth record, (ii) In Ireland the source data will be the National

Perinatal Reporting System (NRPS http://www.esri.ie/health_information/nprs), (iii) In Northern Ireland, the source data will be the Northern Ireland maternity Statistics database (NIMATS), (iv) In England and Wales, the source data will be the ONS, or other relevant body. Data will be collected retrospectively on an annual basis from all sources. We will assume that data unavailable four months after the woman delivered is likely to be unobtainable (but see note in Study Design section above). Thus, data on the first year of the study will be collected at month 16; data on the second year will be collected at month 28 etc.

Data are routinely collected. A formal request for data access will be made at the start of the study. This will require (i) in Scotland – Privacy Advisory Committee approval and a formal approach to NHS Scotland Information Services Division (ISD) (ii) in Ireland a formal approach to NRPS (iii) NIMATS in Northern Ireland (iv) in England and Wales a formal approach will be made to the relevant bodies.

Data will then be sent to the electronic Data Research and Innovation Service (eDRIS) National Safe Haven (NHS National Services Scotland) by secure file transfer protocol (or other similar) for storage and subsequent analysis within a secure project area (dedicated to the AFFIRM study). Further information on the National Safe Haven is available at http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven. Briefly, the National Safe Haven is located on a secure server, in which trusted and authorised researchers can analyse individual level data while maintaining the utmost confidentiality. It is anticipated that all study analysis will be done within the Safe Haven, using one of the available statistical packages (e.g. R, SPSS).

Identifiers on Scottish data within the National Safe Haven are concealed from researchers. Data from outwith Scotland will be anonymised before submission to the National Safe Haven. We propose that data submitted to the National Safe Haven will be “anonymised” by the data provider. However, we propose that the

anonymisation link will be retained at the source so that it will be possible to re-link data retrospectively. The rationale for retaining the ability of local data guardians to re-link data is because it is important to retain the possibility of identifying individual patients retrospectively. Examples include: (i) It is possible that some additional important data may be available at a late stage on individual participants – e.g. in the scenario where the woman or baby had a major adverse event and spent a long time in hospital before discharge or death and (ii) Although our protocol and outcome analysis does not require identifiable data, we believe this will be a 'once in a lifetime" study, and that subsequent secondary analyses could yield important information for patients and for policy makers. If retrospective identification is not possible, this will limit further analysis. One likely example of future analyses is to determine the effect of the intervention on different causes of stillbirth. This is outwith the scope of the current protocol, but could be done relatively straightforwardly, by linking nationally recorded information on "cause" of stillbirth to our study database. We anticipate that such additional analyses would require additional ethics approval, but without a process by which to re-link data, it will not be possible to perform such subsequent analyses.

All Investigators and study site staff involved with this study will comply with the requirements of the Data Protection Act 1998 (or equivalent for those outwith the UK) with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Published results will not contain any personal data that could allow identification of an individual participant.

In addition to the data recorded above, all sites will be asked to provide a copy of their guidelines around (i) maternal awareness of RFM and (ii) management of women presenting with RFM. Copies of guidelines will be sought by the study office (a) at the start of the study (b) immediately before initiation of the intervention in each specific unit and (c) six months after initiation of the intervention in each specific unit.

For the nested qualitative study, we will perform interviews of healthcare workers and a small nested cohort of pregnant women about their experiences of fetal movement and of this intervention. We shall ensure a diversity of age and include nulliparous and multiparous women (n=30 in total). Ten interviews will be conducted with each of the following groups of health care providers: obstetricians, midwives and sonographers/radiologists. The interviews will take a semi-structured format (sensitising and piloting interviews will be conducted prior to the commencement of the trial and in the first month of the nested qualitative study). This format will ensure the same categories of data will be obtained from each participant but also allow individual responses to be fully explored.

STATISTICS AND DATA ANALYSIS

Sample size calculation

The sample size is the number of women delivering in hospitals participating in the study. This was initially planned to include sites in Scotland, totalling around 58,000 deliveries per year with 16 consultant led maternity units, 20 smaller units each delivering less than 350 babies per year, and seven units delivering less than five births per year. The units involved in Perinatal Ireland (an all-Ireland research consortium across 7 academic sites in Ireland currently funded by the Health Research Board, Ireland) have 50,000 births per year with seven large sites. Combining one or two of the smaller units and one larger unit into a single “hospital group” for each local area could provide 24 hospital “groups” – the details of hospital groupings will be reviewed and finalised immediately prior to randomisation. In total, 36 sites expressed interested in participating in the study, although 2 were unable to participate in the study and withdrew before randomisation. In total, 34 units were randomised, these were situated throughout the UK and Ireland (10 in England, 4 in Ireland, 15 in Scotland and 5 in Wales) with 143,140 births per annum.

We calculated statistical power using the methodology for stepped wedge designs proposed in Hussey and Hughes (2007) [37]. First, we analysed stillbirth event data from the Scottish Perinatal and Infant Mortality and Morbidity Report (SPIMMR) covering years 2005-2010 [16] to determine estimates of between- and within-unit variability in stillbirth rate. Analysis was by generalized linear mixed model for binary outcomes. The power calculation, as per equations (#7) and (#8) in [37] assumed: significance level 5%; analysis by generalized linear mixed model; deliveries equally distributed across hospital groupings; baseline stillbirth rate 0.438% [16]; between-cluster variance 0.00816.

Finally, the statistical power depends on the number of groups in which the intervention is implemented at each stage of the stepped wedge design and the duration of recruitment at each "step". Our study design proposes sequential introduction of the intervention into three hospital groups at a time at four month intervals over a 32 month period. It is anticipated that unavailability of data and women asking to withdraw their data will be less than 1%. This would give 89.9% power to detect a 30% relative risk reduction under the intervention and 77.0% power to detect a 25% reduction. A 30% risk reduction was seen in the Norwegian study; the anticipated effect sizes of 25% and 30% relative reduction take into account that the intervention will not have the power to reduce all stillbirths, since 20% of stillbirths in Ireland [38] and 15% in Scotland [16] are associated with congenital anomaly.

Proposed analyses

For the binary primary and secondary outcomes, data will be analysed by generalized linear mixed model with a random effect for hospital and fixed effects for the intervention implementation, study time period and calendar year. A site by intervention interaction random effect will be included in the model and retained if it explains an important proportion of the variability in outcomes. The primary analysis of data will be on an intention to treat basis (the design of the trial means it is not

possible to determine individual patient /caregiver compliance with the intervention). An “on treatment” variable will be calculated for which women will be grouped as active or control according to when the intervention was actually implemented in their site, instead of when the site was randomised to implement the intervention. The primary outcome will be reanalysed using the “on treatment” classification in a sensitivity analysis. There are no planned imputations for missing data. However, if the missing data rate for smoking status during pregnancy is relatively high an imputation technique will be devised. The imputation method will be informed using smoking history at booking and age at delivery [39]. A pre-specified subgroup analysis will be performed for babies with and without congenital anomalies, and will be implemented by testing for an intervention by congenital anomaly interaction added to the generalised linear mixed model described above. No formal interim analyses for efficacy or safety will be performed. A full statistical analysis plan was finalised and signed on 05/10/2016.

Qualitative Data

For the nested qualitative study, the data will be audio recorded and transcribed. The data will be coded thematically and an analytical framework developed to make sense of patient experience of fetal movement and the intervention and also health care providers’ perspectives and experiences. NVivo will be utilised to support the analysis.

Process outcomes

The process outcomes being assessed by the (rates of induction of labour, number of women presenting with reduced fetal movements, interval between perceiving fetal movements and presenting to hospital) will be analysed using the same methods as for the main trial, with the exception of the continuous outcome (interval between perceiving fetal movements and presenting to hospital) which will be analysed using a normal linear mixed model.

ADVERSE EVENTS

This is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) so adverse events will not be formally reported. Stillbirth and other measures of fetal and maternal morbidity are outcomes of the study. The purpose of the intervention is to reduce such adverse events. Therefore, due to the low risks for this trial, a separate DMC is not required and the Trial Steering Committee (TSC) will cover any responsibilities normally allocated to a DMC. If considered necessary, the TSC may review unblinded data for the study, including morbidity and mortality indices. No other adverse event reporting will be undertaken.

TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

The trial will be coordinated by a Project Management Group, consisting of the grant holders and the Trial Manager. The Chief Investigator (JN) will lead the project management group. The Trial Manager will oversee the study and will be accountable to the Chief Investigator. A TSC will be established to oversee the conduct and progress of the trial. The terms of reference and a draft template for reporting will be ratified in one of the early meetings of the TSC.

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the co-sponsors (ACCORD: Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian, Sponsor contact: ray.french@ed.ac.uk), research ethics committee (REC) review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

Study monitoring and audit

The sponsor determined that as no individual participants were recruited to the intervention, and it was not a clinical trial of an investigational medicinal product (CTIMP) no formal monitoring and audit was required.

Good Clinical Practice and Ethical Conduct

The study will be conducted in accordance with the principles of the research governance framework operational and good clinical practice in the relevant country. A favorable ethical opinion has been obtained from the Scotland A REC (Reference 13/SS/0001) and local research and development approval has been obtained prior to commencement of the study.

Local study investigator(s) will be appointed to each site (or for small units, groups of sites). S/he will be responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments.

STUDY CONDUCT RESPONSIBILITIES

Protocol amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, will be reviewed and approved by the Chief Investigator and Sponsor. Amendments to the protocol will be submitted in writing to the appropriate REC and local Research and Development (R&D) department for approval prior to participants being enrolled into an amended protocol.

Protocol violations and deviations

Investigators will not implement any deviation from the protocol without agreement from the Chief Investigator and appropriate REC and R&D department approval except where necessary to eliminate an immediate hazard to trial participants. In the event that an Investigator needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded. If this necessitates a subsequent protocol amendment, this will be submitted to the REC, and local R&D department for review and approval if appropriate.

Serious breach requirements

A serious breach is one which is likely to effect to a significant degree (a) the safety or physical or mental integrity of the participants of the trial; or b) the scientific value of the trial. If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) will be notified within 24 hours. It will be the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and, if so, report it to the REC.

All violations will be assessed by the sponsor(s) to ascertain if they meet the criteria for a serious breach. If the sponsor(s) deem the incident to be a violation that does not constitute a serious breach from the protocol when identified, corrective and preventative actions will be taken where appropriate and they will be recorded in file notes, held within the TMF and ISF.

Study record retention

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

End of study

The end of study date was finalised in the protocol after the study commenced; the agreed end of study date is 31/12/2016. The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with good clinical practice guidelines. The clinical study report will be used as the basis for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

DISCUSSION

The data provided by this study will inform the management of women with reduced fetal movements; which has been recurrently identified by Confidential Enquiries into antepartum stillbirths as suboptimal [33] [34]. This will provide much needed robust evidence to determine whether increased maternal awareness of reduced fetal

movements combined with a standardised management protocol to identify acute or chronic fetal compromise can reduce stillbirth [27].

PEER REVIEW

This project has been peer reviewed internally, and was externally peer reviewed during the process of securing funding from the Chief Scientist's Office of the Scottish Government, Tommy's and Sands.

FUNDING

The AFFIRM study is investigator initiated and funded by Chief Scientist Office, Scottish Government (CZH/4/882), Tommy's and Sands, the Stillbirth and Neonatal Death Charity. CJW was supported in this work by NHS Lothian via the Edinburgh Clinical Trials Unit. AEPH is supported by a Clinician Scientist fellowship from the National Institute for Health Research (NIHR; CS-2013-009). This protocol presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the support of Perinatal Ireland and Dr Mary Higgins (University College Dublin, National Maternity Hospital, Dublin).

CONTRIBUTIONS

Contributors AEPH, CJW, SJES, CJC, SCB, MRD, SW and JEN were involved in developing the trial design. AEPH, CJW, SJES, AR and JEN were involved in drafting and revision of the article. CJW and AR were involved in drafting the statistical aspects of the protocol. JS provided feedback on behalf of a stakeholder

organisation. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS, SW and JEN were involved in preparing the overall study design. AEPH, JEN and MRD prepared education videos for online training. AEPH, SJES, SJS, MG, AH, FMM and JEN facilitated recruitment of sites. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS, SW and JEN will be involved in the collection, management, analysis and interpretation of data and final writing of the trial report.

COMPETING INTERESTS

None declared.

ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
BMI	Body Mass Index
CTG	Cardiotocograph
CTIMP	Clinical Trial of an Investigational Medicinal Product
ECTU	Edinburgh Clinical Trials Unit
FGR	Fetal growth restriction
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Social Care Excellence
NIHR	National Institute for Health Research
NIMATS	Northern Ireland Maternity Statistics database
NRPS	National Perinatal Reporting System
ONS	Office of National Statistics
PSANZ	Perinatal Society of Australia and New Zealand
RCOG	Royal College of Obstetricians and Gynaecologists
R&D	Research and Development
REC	Research Ethics Committee
RFM	Reduced Fetal Movements
SPIMMR	Scottish Perinatal and Infant Mortality and Morbidity Report
TMF	Trial Master File
TSC	Trial Steering Committee
WHO	World Health Organisation

REFERENCES

1. Still-Birth Definition Act Great Britain Curr Law Statut Annot GB, 1992:1.
2. Flenady V, Wojcieszek AM, Middleton P, Ellwood D, Erwich JJ, Coory M, et al. Stillbirths: recall to action in high-income countries. *Lancet* 2016;387(10019):691-702.
3. Flenady V, Koopmans L, Middleton P, Froen JF, Smith GC, Gibbons K, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet* 2011;377(9774):1331-40.
4. Manktelow BM, Smith LK, Seaton SE, Hyman-Taylor P, Kurinczuk JJ, Field DJ, et al. Perinatal Mortality Surveillance Report - UK Perinatal Deaths for births from January to December 2014. Leicester:: The Infant Mortality and Morbidity Group, Department of Health Sciences, University of Leicester., 2016.
5. Lawn JE, Blencowe H, Pattinson R, Cousens S, Kumar R, Ibiebele I, et al. Stillbirths: Where? When? Why? How to make the data count? *Lancet* 2011;377(9775):1448-63.
6. Flenady V, Middleton P, Smith GC, Duke W, Erwich JJ, Khong TY, et al. Stillbirths: the way forward in high-income countries. *Lancet* 2011;377(9778):1703-17.
7. Heazell AE, Whitworth MK, Whitcombe J, Glover SW, Bevan C, Brewin J, et al. Research priorities for stillbirth: process overview and results from UK Stillbirth Priority Setting Partnership. *Ultrasound Obstet Gynecol* 2015;46(6):641-7.
8. Heazell AE, Froen JF. Methods of fetal movement counting and the detection of fetal compromise. *J Obstet Gynaecol* 2008;28(2):147-54.
9. Stacey T, Thompson JM, Mitchell EA, Ekeroma AJ, Zuccollo JM, McCowan LM. The Auckland Stillbirth study, a case-control study exploring modifiable risk factors for third trimester stillbirth: methods and rationale. *The Australian & New Zealand journal of obstetrics & gynaecology* 2011;51(1):3-8.

10. Warland J, O'Brien LM, Heazell AE, Mitchell EA. An international internet survey of the experiences of 1,714 mothers with a late stillbirth: the STARS cohort study. *BMC pregnancy and childbirth* 2015;15:172.

11. Warrander LK, Heazell AE. Identifying placental dysfunction in women with reduced fetal movements can be used to predict patients at increased risk of pregnancy complications. *Medical hypotheses* 2011;76(1):17-20.

12. Vintzileos AM, Fleming AD, Scorza WE, Wolf EJ, Balducci J, Campbell WA, et al. Relationship between fetal biophysical activities and umbilical cord blood gas values. *Am J Obstet Gynecol* 1991;165(3):707-13.

13. Warrander LK, Batra G, Bernatavicius G, Greenwood SL, Dutton P, Jones RL, et al. Maternal perception of reduced fetal movements is associated with altered placental structure and function. *PloS one* 2012;7(4):e34851.

14. Holm Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Froen JF. Maternal characteristics and pregnancy outcomes in women presenting with decreased fetal movements in late pregnancy. *Acta Obstet Gynecol Scand* 2009;88(12):1345-51.

15. Ptacek I, Sebire NJ, Man JA, Brownbill P, Heazell AE. Systematic review of placental pathology reported in association with stillbirth. *Placenta* 2014;35(8):552-62.

16. Healthcare Improvement Scotland. Scottish Perinatal and Infant Mortality and Morbidity Report 2010. Edinburgh: Healthcare Improvement Scotland, 2012.

17. Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. *BMJ (Clinical research ed* 2005;331(7525):1113-7.

18. Saastad E, Winje BA, Stray Pedersen B, Froen JF. Fetal movement counting improved identification of fetal growth restriction and perinatal outcomes--a multi-centre, randomized, controlled trial. *PloS one* 2011;6(12):e28482.

19. Mangesi L, Hofmeyr GJ, Smith V, Smyth RM. Fetal movement counting for assessment of fetal wellbeing. *Cochrane Database Syst Rev* 2015(10):CD004909.

20. Grant A, Elbourne D, Valentin L, Alexander S. Routine formal fetal movement counting and risk of antepartum late death in normally formed singletons. *Lancet* 1989;2(8659):345-9.

21. National Institute for Health and Clinical Excellence. Clinical Guideline 62 - Antenatal care: routine care for the health pregnant woman. London: National Institute for Health and Clinical Excellence, 2008.

22. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al. Reduction of late stillbirth with the introduction of fetal movement information and guidelines - a clinical quality improvement. *BMC pregnancy and childbirth* 2009;9:32.

23. Preston S, Mahomed K, Chadha Y, Flenady V, Gardener G, MacPhail J, et al. Clinical practice guideline for the management of women who report decreased fetal movements. Brisbane,: Australia and New Zealand Stillbirth Alliance, 2010.

24. Royal College Of Obstetricians and Gynaecologists. Management of Reduced Fetal Movements. London: RCOG, 2011.

25. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al. Erratum to: Reduction of late stillbirth with the introduction of fetal movement information and guidelines - a clinical quality improvement. *BMC pregnancy and childbirth* 2010;10:49.

26. Froen JF, Heazell AE, Tveit JV, Saastad E, Fretts RC, Flenady V. Fetal movement assessment. *Seminars in perinatology* 2008;32(4):243-6.

27. Hofmeyr GJ, Novikova N. Management of reported decreased fetal movements for improving pregnancy outcomes. *Cochrane Database Syst Rev* 2012;4:CD009148.

28. Froen JF, Tveit JV, Saastad E, Bordahl PE, Stray-Pedersen B, Heazell AE, et al. Management of decreased fetal movements. *Seminars in perinatology* 2008;32(4):307-11.

29. Dutton PJ, Warrander LK, Roberts SA, Bernatavicius G, Byrd LM, Gaze D, et al. Predictors of poor perinatal outcome following maternal perception of reduced fetal movements--a prospective cohort study. *PloS one* 2012;7(7):e39784.

30. Royal College Of Obstetricians and Gynaecologists. The Investigation And Management Of The Small-For-Gestational-Age Fetus. London: RCOG, 2013.

31. Heazell AE, Green M, Wright C, Flenady V, Froen JF. Midwives' and obstetricians' knowledge and management of women presenting with decreased fetal movements. *Acta Obstet Gynecol Scand* 2008;87(3):331-9.

32. Jokhan S, Whitworth MK, Jones F, Saunders A, Heazell AE. Evaluation of the quality of guidelines for the management of reduced fetal movements in UK maternity units. *BMC pregnancy and childbirth* 2015;15:54.

33. Confidential Enquiry into Stillbirths and Deaths in Infancy. 8th Annual Report, 1 January–31 December 1999. London: Maternal and Child Health Research Consortium, 2001.

34. Draper ES, Kurinczuk JJ, Kenyon S, MBRRACE-UK. obo. MBRRACE-UK Perinatal Confidential Enquiry: Term, singleton, normally formed, antepartum stillbirth. Leicester: The Infant Mortality and Morbidty Studies, Department of Health Sciences, University of Leicester, 2015.

35. Saastad E, Winje BA, Israel P, Froen JF. Fetal movement counting--maternal concern and experiences: a multicenter, randomized, controlled trial. *Birth* 2012;39(1):10-20.

36. Saastad E, Israel P, Ahlborg T, Gunnes N, Froen JF. Fetal movement counting--effects on maternal-fetal attachment: a multicenter randomized controlled trial. *Birth* 2011;38(4):282-93.

37. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials* 2007;28(2):182-91.

38. ESRI Health Research and Information Division. Perinatal Statistics Report 2009, 2011.

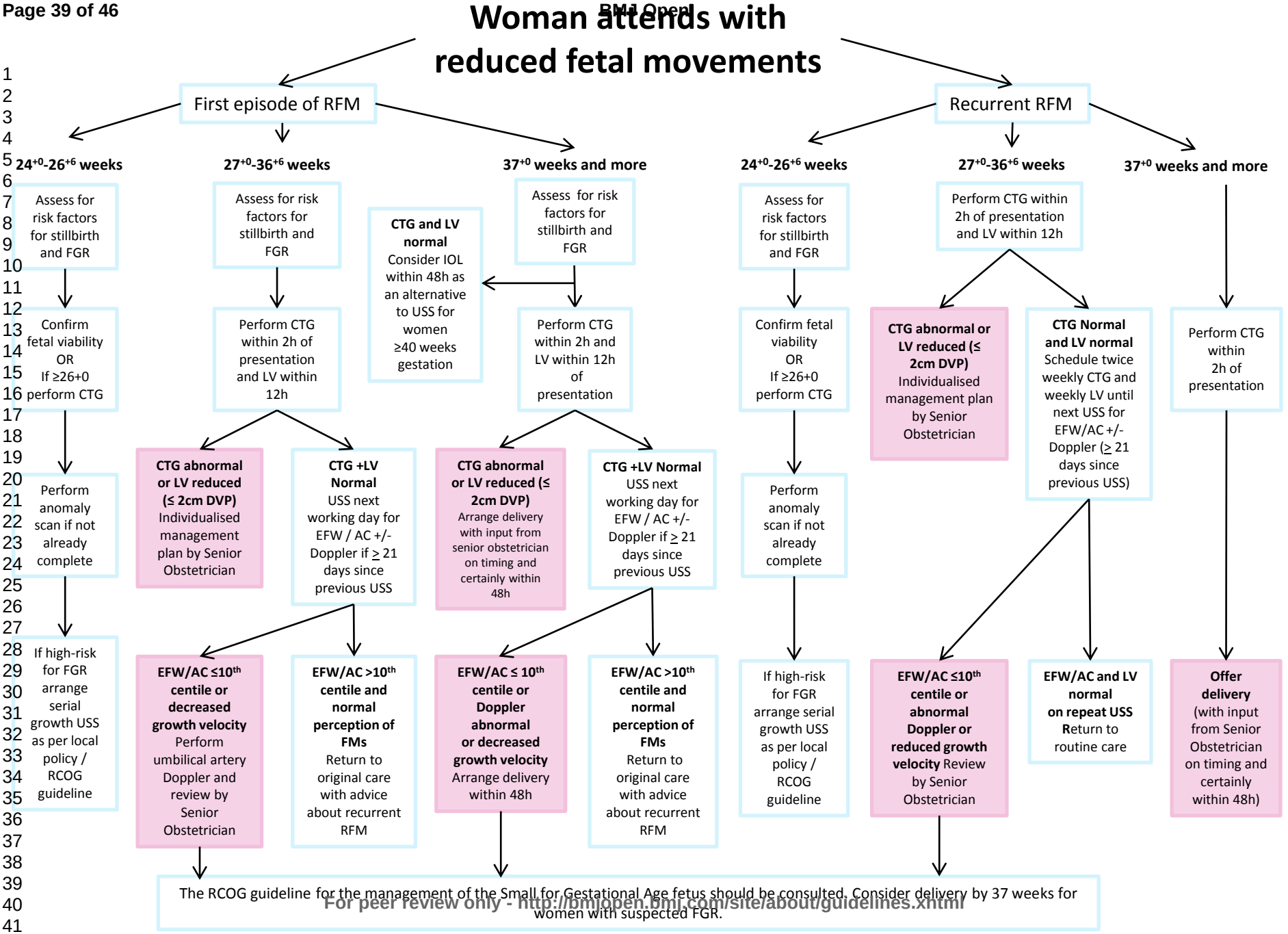
39. Tominey E. Maternal smoking during pregnancy and early child outcomes. Discussion Paper no. 828. London: Centre for Economic Performance, London School of Economics., 2007.

FIGURE LEGENDS

Figure 1 - Stepped wedge design. The shaded areas indicate periods in which the interventions are being implemented. The order in which hospital groupings implement the interventions will be determined via randomization.

Figure 2 – Flow chart for the management of women presenting with reduced fetal movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal movement, USS - ultrasound scan.

Hospital groupings	Months since Start of Trial								
	1-4	5-8	9-12	13-16	17-20	21-24	25-28	29-32	33-36
1-3									
4-6									
7-9									
10-12									
13-15									
16-18									
19-21									
22-24									



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____Page 1____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____Page 4____
	2b	All items from the World Health Organization Trial Registration Data Set	_Included throughout protocol_
Protocol version	3	Date and version identifier	_____Page 4 ____
Funding	4	Sources and types of financial, material, and other support	____Page 28__
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_Names and affiliations Page 1 and 2; Contributions Page 28_
	5b	Name and contact information for the trial sponsor	____Page 24___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_Not applicable__

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____Page 24___
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__Pages 5-11___
	6b	Explanation for choice of comparators	__Pages 8-9____
Objectives	7	Specific objectives or hypotheses	__Pages 11-12__
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	__Pages 13- 14 and Figure 1 ____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__Pages 13 & 16_
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__Pages 14-15___
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__Pages 17-18 and Figure 2___
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	__Not applicable in AFFIRM trial__
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__Pages 17-18___
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__Not applicable_

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__Pages 12-13___
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Randomisation by site explained in Figure 1 and Pages 13-14___
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__Pages21-22 __
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__Page 22 _____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__Page 17 _____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__Page 17 _____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__Page 17 ____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__Page 17 ____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_ Not applicable in AFFIRM study___

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__Pages 18-21___
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__Not applicable_
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__Pages 19-20__
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__Pages 22-23___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__Page 23_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__Pages 22-23__

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_DMC not required, explanation Pg 24___
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__Pages 18, 25-26__
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__Page 24_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__Page 13_____

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___Page 25_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___Page 25_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___Page 25_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__Not applicable_
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__Page 20_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__Page 29_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__Page 27_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__Page 24_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__Page 27____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__Page 28 ____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Not applicable_

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Not Applicable__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_Not Applicable__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

WHO TO CONTACT IF YOU ARE CONCERNED:

(space for sticky with local contact information)

APS Group Scotland
DPPAS33137
Version 3 March 2015

In touch with YOUR BABY

A guide to your baby's movements during pregnancy

Why are my baby's movements important?

Why are we asking women to get to know their baby's movements?

One of the easiest ways to tell if your baby is healthy is to be aware of how much he or she is moving. Every baby is different and we are asking women to take time to become familiar with their baby's own individual pattern of movements. A reduction or change in **your** baby's movements is what is important.

What can affect my baby's movements?

You are less likely to be aware of your baby's movements when active or busy. Some drugs e.g. strong pain relief or sedatives can get into an unborn baby's circulation and affect the movements. Alcohol and smoking (active and passive smoking) may also affect the baby.

Why are my baby's movements important?

If you notice your baby is moving less than usual, or the pattern of movements has changed, this could be the first sign that your baby may not be well or is not growing properly in the womb. Research has shown that a reduction in the baby's movements may indicate an increased risk of stillbirth. You may hear your midwife or doctor referring to 'reduced fetal movement', or RFM for short.

What are the risks of stillbirth?

Stillbirth affects one in 200 babies after 24 weeks gestation and is one of the most common of the serious complications of pregnancy, affecting the lives of around 4,000 families every year in the UK.

One of the easiest ways to tell if your baby is healthy is to see how much he or she is moving. This booklet tells you what to look out for during your pregnancy.

Every baby is different. It is good to get to know your baby's own movements and the pattern of their sleeping and waking and report to us if you notice a reduction in these movements.

18-24 WEEKS

Most women begin to feel their baby move between 18-24 weeks. At first it may feel like 'bubbles', 'flutterings' or 'like trapped wind'. These are often very short and stop and start. It might take you a little while to be sure what you are feeling. But you will soon get to know the feelings. If this is your second baby, you will know what to look out for and may recognise your baby moving sooner.

Everyone is different when it comes to their movements. There are many reasons you might not feel movements as early as you expect. This includes your body weight, the position of your baby and the location of your placenta. What is important is your baby is growing well. Your midwife will be able to discuss this with you further at your 22 week check.

Try to get to know the times of the day when you are most likely to feel your baby move.

24-36 WEEKS

You will have your own way of describing your baby's own movements. Women often describe their baby's movements as 'rolling', 'kicking', 'pushing', 'jabs', 'elbowing' and 'stretches'.

Between 24-36 weeks you will start to recognise your baby's movements more quickly and become more used to the feeling. It is usually easier to feel your baby's movements when you are lying down, e.g. at night time. It is harder to feel your baby move when you are on your feet and moving around.

Try to get to know the times of the day you are most likely to feel your baby move. This will help you to know if he or she is moving less than normal or if movements have stopped.

Occasionally your baby will get hiccups. These do not count as movements. If you are unsure what you should expect when your baby hiccups, speak to your midwife.

BMJ Open

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014813.R1
Article Type:	Protocol
Date Submitted by the Author:	10-Jan-2017
Complete List of Authors:	Heazell, Alexander; University of Manchester, Maternal and Fetal Health Research Centre Weir, Christopher; University of Edinburgh, MRC Hub for Trials Methodology Research; Edinburgh Clinical Trials Unit Stock, Sarah; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health,; School of Women's and Infants' Health, University of Western Australia, Crawley WA 6009. (FMM) Calderwood, Catherine; The Scottish Government St Andrew's House, EH1 3DG., Chief Medical Officer for Scotland, CunninghamBurley, Sarah; University of Edinbrugh, Public Health Sciences Froen, Frederik; Nasjonalt folkehelseinstitutt, Division of Epidemiology Geary, Michael; Rotunda Hospital, Parnell Square Hunter, Alyson; Royal Maternity Hospital, Grosvenor Road, BT12 6BB McAuliffe, Fionnuala; University College Dublin, Murdoch, Edile; Royal Infirmary of Edinburgh, NHS Lothian, EH16 4SA., Department of Neonatology Rodriguez, Aryelly; University of Edinburgh, (ECTU) Edinburgh Clinical Trials Unit Ross-Davie, Mary; NHS Education for Scotland, 3rd Floor, Hanover Buildings, 66 Rose Street, EH2 2NN. Scott, Janet; Sands, Victoria Charity Centre, Suite GF2 Ground Floor, 11 Belgrave Road, SW1V 1RB. Whyte, Sonia; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health, Norman, Jane; , Queen's Medical Research Institute, EH16 4TJ
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Research methods
Keywords:	Reduced Fetal Movements, Perinatal Mortality, Stillbirth, Neonatal Death, Fetal Growth Restriction

Study Protocol

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

Alexander E P HEAZELL,[1,2] alexander.heazell@manchester.ac.uk

Christopher J WEIR, [3,4] christopher.weir@ed.ac.uk

Sarah J E STOCK,[5 6] sarah.stock@ed.ac.uk

Catherine J CALDERWOOD,[7] catherine.calderwood@scotland.gsi.gov.uk

Sarah CUNNINGHAM-BURLEY,[4] sarah.c.burley@ed.ac.uk

J Frederik FROEN,[8] frederik.froen@fhi.no

Michael GEARY,[9] mppgeary@gmail.com

Alyson HUNTER,[10] alyson.hunter@belfasttrust.hscni.net

Fionnuala M MCAULIFFE,[11] fionnuala.mcauliffe@ucd.ie

Edile MURDOCH,[12] edile.murdoch@nhslothian.scot.nhs.uk

Aryelly RODRIGUEZ,[3,4] aryelly.rodriguez@ed.ac.uk

Mary ROSS-DAVIE,[13] mary.ross-davie@nes.scot.nhs.uk

Janet SCOTT [14] janet.scott@uk-sands.org

Sonia WHYTE [5] sonia.whyte@ed.ac.uk

Jane E NORMAN.[5] jane.norman@ed.ac.uk

1. Maternal and Fetal Health Research Centre, Institute of Human Development, University of Manchester. 2. St. Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, M13 9WL. 3. Edinburgh Clinical Trials Unit, Edinburgh, UK 4. Centre for

Population Health Sciences, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG. 5. Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health, Queen's Medical Research Institute, Edinburgh, EH16 4TJ.6. School of Women's and Infants' Health, University of Western Australia, Crawley WA 6009. (FMM) 7. Chief Medical Officer for Scotland, The Scottish Government St Andrew's House Edinburgh EH1 3DG. 8. Department of International Public Health, Norwegian Institute of Public Health, PB 4404 Nydalen, N-0403 Oslo, Norway, 9. Rotunda Hospital, Parnell Square, Dublin 1, Ireland. 10. Centre for Fetal Medicine, Royal Maternity Hospital, Grosvenor Road, Belfast, BT12 6BB 11. UCD Obstetrics & Gynaecology, School of Medicine, University College Dublin, Ireland. National Maternity Hospital, Dublin, Ireland. 12. Department of Neonatology, Royal Infirmary of Edinburgh, NHS Lothian, Edinburgh, EH16 4SA. 13. NHS Education for Scotland, 3rd Floor, Hanover Buildings, 66 Rose Street, Edinburgh EH2 2NN. 14. Sands, Victoria Charity Centre, Suite GF2 Ground Floor, 11 Belgrave Road, London, SW1V 1RB.

Abstract

Background - In 2013, the stillbirth rate in the UK was 4.2 per 1,000 live births, ranking 24th out of 49 high-income countries, with an annual rate of reduction of only 1.4% per year. The majority of stillbirths occur in normally formed infants, with (retrospective) evidence of placental insufficiency the commonest clinical finding. Maternal perception of reduced fetal movements (RFM) is associated with placental insufficiency and increased risk of subsequent stillbirth.

This study will test the hypothesis that the introduction of a package of care to increase women's awareness of the need for prompt reporting of RFM and standardised management to identify fetal compromise with timely delivery in confirmed cases, will reduce the rate of stillbirth. Following the introduction of a similar intervention in Norway the odds of stillbirth fell by 30%, but the efficacy of this intervention (and possible adverse effects and implications for service delivery) have not been tested in a randomised trial.

Methods - We describe a stepped wedge cluster trial design, in which participating hospitals in the UK and Ireland will be randomized to the timing of introduction of the care package. Outcomes (including the primary outcome of stillbirth) will be derived from detailed routinely collected maternity data, allowing us to robustly test our hypothesis. The degree of implementation of the intervention will be assessed in each site. A nested qualitative study will examine the acceptability of the intervention to women and health care providers and identify process issues including barriers to implementation.

Discussion - The data provided by this study will inform the management of women with RFM; which has been recurrently identified as suboptimal in cases of stillbirth. This will provide robust evidence to determine whether increased maternal awareness of RFM combined with a standardised management protocol to identify acute or chronic fetal compromise can reduce stillbirth.

Trial Registration

www.clinicaltrials.gov NCT01777022

Version

Protocol Version 4.2, 19th December 2016

Keywords

Reduced Fetal Movements; Perinatal Mortality; Stillbirth; Neonatal Death; Fetal Growth Restriction.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This trial directly addresses the need for studies of the information given to women regarding fetal movements and the subsequent management of reduced fetal movements identified by Confidential Enquiries into Antepartum Stillbirths, Systematic Reviews and the Stillbirth Priority Setting Partnership.
- A stepped-wedge cluster trial design in combination with routinely collected maternity data allows the trial to be adequately powered to detect a difference in stillbirth as a primary outcome.
- The pragmatic nature of the study represents the potential impact of the introduction of such standardised care into clinical practice.
- The nested qualitative study will provide information regarding the acceptability of the intervention and identify barriers and facilitators to its adoption.
- The lack of information on resource use before and throughout the study period limits the ability to understand the consequences of the intervention on maternity unit workload.

INTRODUCTION

Stillbirth

Stillbirth, defined in the UK as a baby with no signs of life after 24 weeks of completed pregnancy [1], remains the major cause of perinatal mortality in high-income environments, with a recent series of papers in the Lancet on stillbirth issue calling for renewed action in this area [2]. There is no single "cause" of stillbirth, and a significant proportion of stillbirths remain unexplained, but fetal growth restriction, maternal hypertension and low socioeconomic status are amongst the identifiable risk factors [3]. The concept that more can be done to reduce stillbirth in the UK and Ireland is supported by data showing a marked variation in rates between resource rich countries, when similar definitions of stillbirth are used [2]. Notably, the UK has a higher rate than comparable resource rich countries such as Germany, Netherlands, New Zealand and Norway with rates in the UK some 50% greater than those of the Netherlands. Disappointingly, the annual rate of reduction in stillbirth from 2000 to 2014 in the UK was only 1.4% compared to 6.8% in the Netherlands and 2.8% in New Zealand [2]. Rates of stillbirth in Scotland (3.7 per 1,000 births in 2014) and Ireland, at (4.4 per 1,000 livebirths in 2013) are similar to rates in England and Wales at 4.2 per 1,000 livebirths (England and Wales, 2014) [4]. The reduction of avoidable harm for women and babies is viewed as a major priority for Government and its agencies throughout the UK and Ireland. Consequently, several initiatives have been developed by national governments in the UK and Ireland including the Scottish Government Stillbirth Working Group, NHS England Saving Babies' Lives Care Bundle and the Welsh Assembly 1000 Lives Plus strategy. These strategies have identified the need for better evidence to guide efforts to prevent stillbirths.

Using a robust priority setting strategy [5] the Lancet Stillbirth's series steering committee identified issues around detection and management of reduced fetal movements (RFM) amongst the top ten key research questions on prevention and

management of stillbirth [6]. This was confirmed in the UK-based Stillbirth Priority Setting partnership involving over 1,700 parents and professionals which identified two relevant issues among the highest ranked research questions regarding stillbirth: i) which investigations identify a fetus at risk of stillbirth after a mother believes she has experienced reduced fetal movements? and ii) would more accessible evidence-based information on signs and symptoms of stillbirth risk, designed to empower women to raise concerns with healthcare professionals, reduce the incidence of stillbirth? [7] Thus, RFM has been identified as a highly-relevant area of study by parents, professionals and researchers.

Reduced Fetal Movements, Stillbirth and Placental Insufficiency

There is a clear association between maternal perception of RFM and late stillbirth dating back over four decades [8]. In a recent series of 2,000 women, the adjusted OR (95% CI) of late stillbirth in women with RFM (compared with controls) was 2.37 (1.29-4.35) [9]. One international study of 1,714 women who experienced a stillbirth found that 30% had noted significant RFM prior to the diagnosis of stillbirth [10]. Although the mechanisms have not been fully delineated, it is likely that RFM and stillbirth are linked by a common pathology, that of placental dysfunction [11]. There is good evidence linking placental dysfunction and RFM. Compared to controls with an active fetus women who have fewer fetal movements on ultrasound scan immediately prior to caesarean section are more likely to have umbilical cord gas measurements indicative of acidaemia, hypoxaemia, and hypercapnia [12]. Women delivering within one week of an episode of RFM show differences in placental structure and function which are reminiscent of those seen in fetal growth restriction (FGR) and stillbirth [13 14]. Additionally, the odds of fetal growth restriction (FGR, defined as being at less than the 10th centile for gestation adjusted birthweight) were greater in women with RFM compared with controls (adjusted OR 1.6, 95% CI 1.1–2.2 [15]). Taken together these

data are strong evidence that placental dysfunction is associated with RFM, and a causative pathway seems likely.

The evidence linking placental dysfunction and stillbirth is even stronger; a systematic review of placental pathology in stillbirths described abnormalities in up to 65% of cases [16]. Amongst the 291 stillbirths in Scotland in 2010, 137 (47%) had evidence of placental dysfunction [17]. Given that the placenta was examined in only 80% of stillbirths, the true prevalence of placental dysfunction is likely to be higher. In addition, between 20%-40% of stillborn babies are reported to have FGR, as defined by a birthweight less than the 10th centile [18]. Additionally, the Lancet report notes that "placental pathologies accounted for one in four deaths across all gestational ages, and were contributory or causal in more than half of cases" [6]. Given that stillbirth is strongly related to placental dysfunction, and RFM is a "biomarker" of placental dysfunction then better management of women presenting with RFM focussing on the detection of placental dysfunction might reduce the risk of stillbirth.

Formal Fetal Movement Counting

Although prenatal detection of FGR is improved by fetal movement counting [19], a systematic review [20], and a large and influential cluster randomised trial (which dominates the systematic review) showed that routine fetal movement counting using the count to ten charts had no effect on perinatal mortality [21]. Thus, the National Institute for Health and Social Care Excellence (NICE) recommended that "Routine formal fetal movement counting should not be offered" [22]. Importantly, the large cluster randomised trial tested a specific alarm limit for RFM, but did not recommend a specific management strategy for women who did present with RFM. There were two important observations from this study, firstly that in both groups the perinatal mortality rate was lower than contemporary or subsequent periods in the UK and secondly that more women in the fetal movement counting arm came in with a live baby who subsequently died compared with the control arm (19 vs 11), suggesting

that one reason the strategy failed to reduce perinatal mortality was inadequate investigation and management of those presenting with RFM [21].

Optimal strategy for determining RFM to prompt maternal presentation to the maternity service

Maternal concern about RFM is a common reason to contact maternity services with between 6-15% of women presenting during the third trimester.[23] [24] Nevertheless, delays in reporting RFM to maternity care providers may increase the risk of adverse outcome.[25] [26] The lack of good-quality information given to women about fetal movements has been highlighted as an example of suboptimal care in Confidential Enquiries into Antepartum Stillbirth.[27] [28] Qualitative studies suggest that women frequently perceive RFM two days prior to the diagnosis of fetal death, and in some cases contractions were misinterpreted as fetal movements.[29] Therefore, giving information to women regarding fetal movements and when they should be concerned about RFM is a key component of an intervention to reduce stillbirth.

However, giving clear information about RFM can be challenging as there is no uniform threshold of fetal movements below which perinatal morbidity increases [24], and no evidence that a specific threshold performs better than maternal perception of reduced fetal movements alone [8]. Current guidelines from the RCOG and PSANZ [30] [31], informed by a large Norwegian study [32] suggest that it is maternal *perception* of decreased fetal movement which is important. Therefore, information for pregnant women in this study (shown in Supplementary File 1) described the importance of fetal movements, the need to get to know normal fetal activity, how fetal movements change in late pregnancy and who to contact if the mother perceives RFM. The educational package aimed to ensure that these messages were reinforced by staff behaviour at antenatal contacts.

Optimal strategy for investigation and management of women presenting with RFM.

A recent systematic review found there are no proven strategies for the investigation and management of women presenting with RFM [33]. Cardiotocography (CTG) is routinely used to ascertain fetal wellbeing, and it is the cornerstone of the RCOG guideline [31]. However, data from Norway, suggests that ultrasound assessment of fetal size is often the most helpful investigation, performing well on both an absolute basis, and compared with other interventions [34]. In a series of over 3,000 women with RFM, ultrasound (including measurement of fetal biometry and liquor volume) was found to be useful in detecting abnormalities in 11.6% of scans. In 71% of women in whom an abnormality was found, ultrasound was the only technique that detected an abnormality. Additionally, 85% of abnormalities detected by ultrasound, were important in informing the clinical management of the woman [34]. These data are supported by a smaller UK study which found that abnormalities detected on CTG or ultrasound scan were most strongly associated with adverse outcome in women with RFM, with identification of abnormal estimated fetal growth centile on scan being the test most highly predictive of poor outcome [35]. Perhaps this is not surprising, given the strong association between RFM and placental dysfunction and the central importance of ultrasound in the identification and management of small for gestational age babies [36]. Given these data, it is concerning that a survey of clinicians in Scotland showed that fewer than 5% would routinely refer women with RFM for ultrasound examination (unpublished data from June 2012), and a survey of 223 UK midwives and obstetricians described that 17.9% of respondents would perform an ultrasound scan [37]. These views of clinicians may reflect the variable quality of local guidelines, which are frequently not based on national recommendations, even those for which there is strong evidence [38].The variation in information given to women and subsequent management of RFM has been highlighted as sources of suboptimal care in two confidential enquiries into antepartum stillbirth [27 28]. Therefore, we believe that current investigation of women presenting with RFM is inadequate, hence using the best available evidence, we have drafted what we consider to be a robust evaluation

protocol for investigation of women with RFM.

Potentially efficacy of a package of intervention for RFM

Supportive data for the package of interventions used in this study (information for women and standardised management protocol) comes from a large observational "clinical quality improvement study" in Norway which found a significant fall in rates of stillbirth (from 3.0/1,000 to 2.0/1,000 [OR 0.67 95% CI 0.48–0.93]) after the introduction of an intervention package consisting of written information for women about awareness of RFM combined with consensus guidelines for health professionals about their management [32]. Although this study was not randomised, and therefore constitutes only level II-3 evidence, it has informed recommendations from the Royal College of Obstetricians and Gynaecologists (RCOG) and Perinatal Society of Australia and New Zealand (PSANZ) that "women should be advised to be aware of their baby's individual pattern of movements and that if they are concerned about a reduction in or cessation of fetal movements …..they should contact their maternity unit" [30 31].Following initial publication of the Norwegian study, a re-analysis was required as discrepancies between stillbirth rates in the study and the Medical Birth Registry of Norway were identified. This reanalysis found the reduction in stillbirth rates was of borderline statistical significance (OR 0.72, 95% CI 0.50-1.03). The authors concluded that further studies were needed to determine whether this approach was associated with a reduction in stillbirth [39].

Importantly, in the Norwegian study, there was no increase in the proportion of women who presented with RFM when rates were compared before and after the intervention [32]. However, women with RFM presented significantly earlier to hospital than they had hitherto, potentially allowing time for intervention to reduce perinatal mortality. These data suggest that a package of interventions encouraging women with RFM to present early to hospital, combined with a structured approach to their management might reduce rates of stillbirth without contributing to a large increase in admissions antenatally.

Potential harms of a package of care around increased awareness and optimised management of RFM

Any clinical intervention which aims to improve outcomes also has the ability to do harm. Thus, it is essential that the intervention proposed is rigorously evaluated using the gold standard technique of a randomised trial, rather than being introduced as a service development. When the study began, there was a small window of opportunity to do this, as the enthusiasm to improve current management of RFM is such that routine introduction of the package of care is unlikely to be delayed much further than the current scheduled end date of this study. Possible harms of a package of care consisting of a management plan for identification and delivery of the "at risk" fetus, together with strategies for increasing pregnant women's awareness of the need to report early include increased maternal anxiety and increased intervention (including hospital admission, induction of labour and Caesarean section) which itself is associated with pregnancy related complications. The available evidence is reassuring on some of these issues. A systematic review of 23 publications from 16 studies found three studies involving 2,030 women addressing maternal concern and an additional three studies involving 1,468 women investigating maternal-fetal attachment. These demonstrated no evidence of increased maternal anxiety and results regarding maternal-fetal attachment were discordant.[40] In the Norwegian service development study, the package of care increased rates of follow up of women, but there was no increase in admissions overall, admissions for induction or admissions for emergency caesarean section [32] – again, whilst reassuring these outcomes require formal evaluation in a randomised and relevant setting to the UK and Republic of Ireland. The final possible harm of the package is around increased resource use, and the opportunity cost of focussing on RFM rather than other potential methods to prevent stillbirth.

RATIONALE

The aim of this study is to test the hypothesis that a package of interventions consisting of strategies for increasing pregnant women's awareness of the need to report early when they perceive a reduction in fetal movements, followed with a management plan for identification and delivery of the "at risk" fetus in such women, will reduce rates of stillbirth.

STUDY OBJECTIVES

Primary Objective

The primary objective is to answer the research question 'Does the introduction of a protocol for detection and management of decreased fetal movements reduce rates of stillbirth?' The secondary objectives are to answer the following research questions:

- What is the effect of the intervention on rates of caesarean section and induction of labour?
- What is the effect of the intervention on rates of admission to the neonatal intensive care unit?
- What is the effect of the intervention on the proportion of women with FGR remaining undelivered by 40 weeks gestation?
- What is the acceptability of such a package of care to pregnant women and their health care providers?
- What other process outcomes are influenced by the intervention, such as health care provider/patient interactions?

ENDPOINTS

Primary Outcome

The primary endpoint is stillbirth (antepartum and intrapartum). We will use the UK definition of stillbirth which is "a baby delivered without signs of life after 23^{+6} weeks" [4]. Where gestation is uncertain we will include all babies with a birth weight of 500g or more.

Secondary Endpoints

Other measures of perinatal mortality including:

- Stillbirth at 37 weeks gestation and above
- Stillbirth at 28 weeks gestation and above (WHO definition of stillbirth)
- Stillbirth at 22 weeks gestation and above (international stillbirth alliance definition)
- Stillbirths amongst normally formed infants of 22 weeks gestation and above, 24 weeks gestation and above, 28 weeks gestation and above and 37 weeks gestation and above.
- Perinatal mortality (defined as stillbirth at 24 weeks gestation and above and deaths in the first seven days of life)
- Rates of caesarean section
- Rates of induction of labour (for any indication)
- Rates of elective delivery (induction of labour and caesarean section prior to the onset of labour) overall
- Rates of induction of labour at 39 weeks gestation or later
- Mean gestation at induction of labour
- Rates of admission to the neonatal unit (and their reasons)

- Rates of admission to the neonatal unit for more than 48 hours
- Rates of admission to the neonatal unit for term babies (those born at 37 weeks 0 days or greater)
- Proportion of infants with fetal growth restriction (less than the 5th centile, customised for gender) remaining undelivered at or after 40 weeks gestation
- Birthweight centile (according to the Intergrowth birthweight centile calculator at https://intergrowth21.tghn.org)
- Rates of spontaneous vaginal delivery

Other secondary outcomes are the baby parameters:

- Gestation at birth
- Proportion of babies born preterm (<37 weeks gestation)
- Gender of the baby
- Birthweight of the baby
- Apgar score at 5 minutes
- Proportion of babies with 5 minute Apgar score < 7
- Proportion of babies with 5 minute Apgar score < 4
- Resuscitation required at birth

We will also collect the following data: maternal age, maternity unit of delivery, birthweight, gestation of delivery, parity, gestation, sex, smoking (current and ever), maternal body mass index (BMI), number of babies (one or more), ethnicity (to allow a customised birthweight centile to be generated), method of delivery, deprivation category (where available) and other neonatal variables including Apgar score and encephalopathy. Adjustment will be made for the following variables: (maternal age,

maternity unit of delivery, parity, smoking status, maternal BMI, number of babies [one or more] and ethnicity)

STUDY DESIGN

This is a multicentre, stepped wedge cluster randomised trial of a package of care consisting of a management plan for identification and delivery of the 'at risk' fetus, together with strategies for increasing pregnant women's awareness of the need to report RFM early. The trial developed from a planned quality improvement project proposed by the Scottish Government to reduce stillbirths. This was planned to emphasise the importance of fetal movement monitoring and was to be rolled out to all NHS maternity units in Scotland. However, prior to this change it was agreed that the roll out could be performed in such a way as to allow the assessment of the effect of the intervention, the stepped-wedge design would be the natural choice in this circumstance.

The study will take place in participating hospitals in the UK and Ireland (a complete list is available http://www.crh.ed.ac.uk/affirm/randomised-hospitals/). A nested qualitative study will examine the acceptability of the intervention to patients and health care providers and identify process issues (barriers to implementation). Clinical audit (detailed in supplementary information 2) conducted after the change in practice will be used to determine the effect of interventions on process outcomes (e.g. number of women presenting with reduced fetal movements, interval between perceiving reduced fetal movements and presentation to hospital, number of ultrasound scans, number of admissions for induction of labour). A diagram indicating randomisation of hospital groupings in the stepped wedge design is shown in Figure 1.

The interventions will be introduced over a 32 month period. Data will be collected over a 36 month period. Data in the 'active phase' after introduction of the intervention will be compared to data in the 'control phase' – the period during which usual care processes in study sites are followed from study start to the time of introduction of the intervention. Given that it will take individual units some time (a) to effect change in management in their unit from time of introduction of the intervention and (b) that it will take some time for this change in practice to impact on clinical outcomes, we plan a "washout" period of two months after the introduction of the intervention during which data will not be included in either group for analysis (Figure 1). Data will be collected four months after the last birth, a further two months has been included for data analysis, giving a total study duration of 42 months.

STUDY POPULATION

Number of participants

Participants will be those delivering at all the sites over the study period (36 months). All eligible women will be recruited to the cluster randomised controlled trial. Based on previous delivery numbers, after accounting for a washout period of two months (and assuming no withdrawals or losses to follow up) this is estimated to be a total of around 143,140 women per annum. A subset of around 30 participating women and 30 midwives, sonographers and obstetricians will be recruited to the nested qualitative study, which is based in the Scottish sites.

Inclusion criteria

We will include all women delivering at one of the participating maternity units for the duration of the study. Women who have been seen at any of the maternity units but who deliver at home will not be included. The duration of the study will be 42 months

from the start of the trial (01/02/2014). For practical reasons, participants for the nested qualitative study will be recruited from the participating units in Scotland.

Exclusion criteria

We will exclude women as follows:

- Women for whom data on delivery outcomes is still unavailable four months after the date of delivery
- Women delivering in the "washout" period in each unit.

Members of the trial management group and participants who do not speak/understand English will be excluded from participating in the nested qualitative study.

Identifying participants

Women will be identified from those whose data is included in routine data returns from each unit. Potential participants for the nested qualitative study will be identified from those attending antenatal clinics in participating hospitals, and/or local staff.

Consenting participants

The main study is a stepped wedge cluster randomised trial of a package of care which would be introduced in many of the participating units regardless of whether the trial was on-going or not and the trial uses only routinely collected data on participants. The ethics committee indicated that formal individual patient consent is not necessary for the main trial. Participants in the nested qualitative study will be asked for individual consent.

Screening for eligibility

As participants are not directly recruited we will not perform any specific screening tests for this aspect of this project. Participants for the nested qualitative study will be: (i) Pregnant women attending hospitals who are participating in the main trial in

Scotland. Purposive sampling will ensure that the final sample set includes women who have and who have not experienced RFM, both before and after the introduction of the intervention; (ii) Hospital staff (including midwives, ultrasonographers and obstetricians/radiologists) working in participating hospitals in Scotland. There will be no specific screening tests for eligibility for the nested qualitative study, except that women who have experienced a stillbirth in the index pregnancy will not be approached.

Ineligible and non-recruited participants

Potential participants for the nested qualitative study who are not approached or who decline will have no specific interventions / procedures.

Withdrawal of Study Participants

The nature of a cluster randomised study is such that it is not possible for the participant to withdraw from the "cluster" unless she changes maternity unit part way through her pregnancy. We plan to collect routinely recorded anonymised data; patients have the right to opt out of having their data used – if this happens their data would be excluded from the study database (e.g. under the Confidentiality and Security advisory Group Report 2002 and the Data Protection Act (1998) requirements for fair processing of data). Participants in the nested qualitative study who wish to withdraw will be allowed to do so. Their data will be retained and used, unless they additionally indicate that they wish to withdraw their data.

RANDOMISATION

Randomisation Procedures

This is a cluster-randomised, stepped-wedge design trial wherein maternity units rather than individual patients are randomised. All units will implement the fetal movement monitoring intervention at some point during the trial; the random element is the time point at which this will occur, the so-called "step" of the stepped-wedge

design. Participating maternity units will be blinded to their randomly allocated time point until the time this is required to be revealed to enable the necessary training in the implementation of the intervention to be delivered. Primary and secondary outcomes of the trial will be gathered in a blinded manner via routinely collected data sources.

Maternity units which are in close proximity to each other will be grouped for the purposes of randomisation. This will assist with the feasibility of delivering the training for and implementation of the intervention. Furthermore, this local synchronisation of the intervention implementation will minimise the chances of contamination (introduction of the intervention prematurely) from maternity units which have already implemented the intervention to those not yet randomised.

The order in which the groups of maternity units step in to implement the intervention will be determined by computer generated random numbers from a uniform distribution. The randomisation list will be held by the Edinburgh Clinical Trials Unit (ECTU). The identities of the research team staff whose roles in the trial require them to be unblinded to randomisation codes will be recorded in the trial master file (TMF).

Treatment Allocation

Participating sites will be randomised to the intervention or conventional clinical management. All units will be providing conventional treatment at baseline according to local practice – this is the treatment established before the study starts. Sites will be randomised to “active” treatment in turn as described above. Active treatment will consist of a package of care consisting of a management plan for identification and delivery of the ‘at risk’ fetus, together with strategies for increasing pregnant women’s awareness of the need to report RFM early. The recommended management plan for identification and delivery of the “at risk” fetus is shown in Figure 2. Practice change in the active units will be achieved by: (i) written/email information to all clinicians (doctors, midwives and ultrasonographers) in each unit about the study protocol and

amendment of the local protocol for Reduced Fetal Movements (RFM) to that of the study protocol; (ii) a short web-based training package taking approximately one hour to complete for all clinicians in each centre and (iii) training /information sessions to run in each unit and (iv) posters in each unit to describe the practice change. Strategies for encouraging clinicians to increase pregnant women's awareness of fetal movement will include all the above and also a fetal movement leaflet for pregnant women (shown in Supplementary Information 1). The Norwegian quality improvement study showed inconclusive results regarding the effect of the intervention in non-European women.[41] To attempt to address this, the AFFIRM information leaflet was available in 12 languages including: Arabic, Bengali, English, Hindi, Hungarian, Latvian, Lithuanian, Mandarin, Polish, Russian and Urdu. Furthermore, by including staff education which highlighted the need to ask women about fetal movements in routine antenatal consultations as many women as possible should have received information about what to do if they perceive RFM.

Once units have begun active treatment it is not anticipated that they will return to conventional treatment. We will conduct an audit of women presenting with reduced fetal movements and assess the proportion of staff completing the online training to assess the extent to which sites have followed the intervention plan. Units will be informed about treatment allocation as near as possible to the implementation of the "active" treatment. For practical purposes, we anticipate that each unit will need around three months' notice before the "active" treatment is introduced, hence units will be informed of the timing of their treatment allocation (step) three months before the active treatment is due to start. The treatment allocation will not be administered blind and there are no restrictions on concomitant care or other interventions during the study, hence there is no need for emergency unblinding and there are no stopping rules for the study.

DATA COLLECTION

For the main trial, data will be accessed from the information routinely collected during the clinical management of the patient. For consistency, we will normally only include data items which become available within four months after the delivery date in question, although we may seek advice from the independently-chaired trial steering committee (TSC) about exceptions as they arise. Different data sources will be used for different regions of the study: (i) In Scotland the source data will be SMR2 and the Scottish Birth record, (ii) In Ireland the source data will be the National Perinatal Reporting System (NRPS http://www.esri.ie/health_information/nprs), (iii) In Northern Ireland, the source data will be the Northern Ireland maternity Statistics database (NIMATS), (iv) In England and Wales, the source data will be the ONS, or other relevant body. Data will be collected retrospectively on an annual basis from all sources. We will assume that data unavailable four months after the woman delivered is likely to be unobtainable (but see note in Study Design section above). Thus, data on the first year of the study will be collected at month 16; data on the second year will be collected at month 28 etc.

Data are routinely collected. A formal request for data access will be made at the start of the study. This will require (i) in Scotland – Privacy Advisory Committee approval and a formal approach to NHS Scotland Information Services Division (ISD) (ii) in Ireland a formal approach to NRPS (iii) NIMATS in Northern Ireland (iv) in England and Wales a formal approach will be made to the relevant bodies.

Data will then be sent to the electronic Data Research and Innovation Service (eDRIS) National Safe Haven (NHS National Services Scotland) by secure file transfer protocol (or other similar) for storage and subsequent analysis within a secure project area (dedicated to the AFFIRM study). Further information on the National Safe Haven is available at http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven. Briefly, the

National Safe Haven is located on a secure server, in which trusted and authorised researchers can analyse individual level data while maintaining the utmost confidentiality. It is anticipated that all study analysis will be done within the Safe Haven, using one of the available statistical packages (e.g. R, SPSS).

Identifiers on Scottish data within the National Safe Haven are concealed from researchers. Data from outwith Scotland will be anonymised before submission to the National Safe Haven. We propose that data submitted to the National Safe Haven will be "anonymised" by the data provider. However, we propose that the anonymisation link will be retained at the source so that it will be possible to re-link data retrospectively. The rationale for retaining the ability of local data guardians to re-link data is because it is important to retain the possibility of identifying individual patients retrospectively. Examples include: (i) It is possible that some additional important data may be available at a late stage on individual participants – e.g. in the scenario where the woman or baby had a major adverse event and spent a long time in hospital before discharge or death and (ii) Although our protocol and outcome analysis does not require identifiable data, we believe this will be a 'once in a lifetime" study, and that subsequent secondary analyses could yield important information for patients and for policy makers. If retrospective identification is not possible, this will limit further analysis. One likely example of future analyses is to determine the effect of the intervention on different causes of stillbirth. This is outwith the scope of the current protocol, but could be done relatively straightforwardly, by linking nationally recorded information on "cause" of stillbirth to our study database. We anticipate that such additional analyses would require additional ethics approval, but without a process by which to re-link data, it will not be possible to perform such subsequent analyses.

All Investigators and study site staff involved with this study will comply with the requirements of the Data Protection Act 1998 (or equivalent for those outwith the UK)

with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Published results will not contain any personal data that could allow identification of an individual participant.

In addition to the data recorded above, all sites will be asked to provide a copy of their guidelines around (i) maternal awareness of RFM and (ii) management of women presenting with RFM. Copies of guidelines will be sought by the study office (a) at the start of the study (b) immediately before initiation of the intervention in each specific unit and (c) six months after initiation of the intervention in each specific unit.

For the nested qualitative study, we will perform interviews of healthcare workers and a small nested cohort of pregnant women about their experiences of fetal movement and of this intervention. We shall ensure a diversity of age and include nulliparous and multiparous women (n=30 in total). Ten interviews will be conducted with each of the following groups of health care providers: obstetricians, midwives and sonographers/radiologists. The interviews will take a semi-structured format (sensitising and piloting interviews will be conducted prior to the commencement of the trial and in the first month of the nested qualitative study). This format will ensure the same categories of data will be obtained from each participant but also allow individual responses to be fully explored.

STATISTICS AND DATA ANALYSIS

Sample size calculation

The sample size is the number of women delivering in hospitals participating in the study. This was initially planned to include sites in Scotland, totalling around 58,000 deliveries per year with 16 consultant led maternity units, 20 smaller units each delivering less than 350 babies per year, and seven units delivering less than five births per year. The units involved in Perinatal Ireland (an all-Ireland research

consortium across 7 academic sites in Ireland currently funded by the Health Research Board, Ireland) have 50,000 births per year with seven large sites. Combining one or two of the smaller units and one larger unit into a single "hospital group" for each local area could provide 24 hospital "groups" – the details of hospital groupings will be reviewed and finalised immediately prior to randomisation. In total, 36 sites expressed interested in participating in the study, although 2 were unable to participate in the study and withdrew before randomisation. In total, 34 units were randomised, these were situated throughout the UK and Ireland (10 in England, 4 in Ireland, 15 in Scotland and 5 in Wales) with 143,140 births per annum.

We calculated statistical power using the methodology for stepped wedge designs proposed in Hussey and Hughes (2007).[42] First, we analysed stillbirth event data from the Scottish Perinatal and Infant Mortality and Morbidity Report (SPIMMR) covering years 2005-2010 [17] to determine estimates of between- and within-unit variability in stillbirth rate. Analysis was by generalized linear mixed model for binary outcomes. The power calculation, as per equations (#7) and (#8) in [42] assumed: significance level 5%; analysis by generalized linear mixed model; deliveries equally distributed across hospital groupings; baseline stillbirth rate 0.438% [17]; between-cluster variance 0.00816.

Finally, the statistical power depends on the number of groups in which the intervention is implemented at each stage of the stepped wedge design and the duration of recruitment at each "step". Our study design proposes sequential introduction of the intervention into three hospital groups at a time at four month intervals over a 32 month period. It is anticipated that unavailability of data and women asking to withdraw their data will be less than 1%. This would give 89.9% power to detect a 30% risk reduction under the intervention and 77.0% power to detect a 25% reduction. A 30% risk reduction was seen in the Norwegian study; the anticipated effect sizes of 25% and 30% relative reduction take into account that the

intervention will not have the power to reduce all stillbirths, since 20% of stillbirths in Ireland [43] and 15% in Scotland [17] are associated with congenital anomaly.

Proposed analyses

For the binary primary and secondary outcomes, data will be analysed by generalized linear mixed model with a random effect for hospital and fixed effects for the intervention implementation and study time period. A site by intervention interaction random effect will be included in the model and retained if it explains an important proportion of the variability in outcomes. The primary analysis of data will be on an intention to treat basis (the design of the trial means it is not possible to determine individual patient /caregiver compliance with the intervention). An "on treatment" variable will be calculated for which women will be grouped as active or control according to when the intervention was actually implemented in their site, instead of when the site was randomised to implement the intervention. The primary outcome will be reanalysed in two sensitivity analyses. Firstly, we will perform the analysis according to the actual timing of the implementation of the intervention rather than the randomised timing of the intervention using the "on treatment" classification. Secondly, we will perform the analysis in the subgroup of sites who were deemed to have implemented the intervention effectively according to the perception of the Principal Investigator at each site. The accuracy of this perception will be confirmed with the findings of a site audit (details in Supplementary Information 2). There will be no attempt to correlate the impact of the intervention according to the results of the site audit.

There are no planned imputations for missing data. However, if the missing data rate for smoking status during pregnancy is relatively high an imputation technique will be devised. The imputation method will be informed using smoking history at booking and age at delivery [44]. A pre-specified subgroup analysis will be performed for babies with and without congenital anomalies, and will be implemented by testing for an

intervention by congenital anomaly interaction added to the generalised linear mixed model described above. No formal interim analyses for efficacy or safety will be performed. A full statistical analysis plan will be finalised prior to locking of the study database.

Qualitative Data

For the nested qualitative study, the data will be audio recorded and transcribed. The data will be coded thematically and an analytical framework developed to make sense of patient experience of fetal movement and the intervention and also health care providers' perspectives and experiences. NVivo will be utilised to support the analysis.

Process outcomes

The process outcomes being assessed by the (rates of induction of labour, number of women presenting with reduced fetal movements, interval between perceiving fetal movements and presenting to hospital) will be analysed using the same methods as for the main trial, with the exception of the continuous outcome (interval between perceiving fetal movements and presenting to hospital) which will be analysed using a normal linear mixed model.

ADVERSE EVENTS

This is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) so adverse events will not be formally reported. Stillbirth and other measures of fetal and maternal morbidity are outcomes of the study. The purpose of the intervention is to reduce such adverse events. Therefore, due to the low risks for this trial, a separate DMC is not required and the Trial Steering Committee (TSC) will cover any responsibilities normally allocated to a DMC. If considered necessary, the TSC may review unblinded data for the study, including morbidity and mortality indices. No other adverse event reporting will be undertaken.

672

TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

The trial will be coordinated by a Project Management Group, consisting of the grant holders and the Trial Manager. The Chief Investigator (JN) will lead the project management group. The Trial Manager will oversee the study and will be accountable to the Chief Investigator. A TSC will be established to oversee the conduct and progress of the trial. The terms of reference and a draft template for reporting will be ratified in one of the early meetings of the TSC.

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the co-sponsors (ACCORD: Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian, Sponsor contact: ray.french@ed.ac.uk), research ethics committee (REC) review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

Study monitoring and audit

The sponsor determined that as no individual participants were recruited to the intervention, and it was not a clinical trial of an investigational medicinal product (CTIMP) no formal monitoring and audit was required.

Good Clinical Practice and Ethical Conduct

The study will be conducted in accordance with the principles of the research governance framework operational and good clinical practice in the relevant country. A favorable ethical opinion has been obtained from the Scotland A REC (Reference

13/SS/0001) and local research and development approval has been obtained prior to commencement of the study.

Local study investigator(s) will be appointed to each site (or for small units, groups of sites). S/he will be responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments.

STUDY CONDUCT RESPONSIBILITIES

Protocol amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, will be reviewed and approved by the Chief Investigator and Sponsor. Amendments to the protocol will be submitted in writing to the appropriate REC and local Research and Development (R&D) department for approval prior to participants being enrolled into an amended protocol.

Protocol violations and deviations

Investigators will not implement any deviation from the protocol without agreement from the Chief Investigator and appropriate REC and R&D department approval except where necessary to eliminate an immediate hazard to trial participants. In the event that an Investigator needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded. If this necessitates a subsequent protocol amendment, this will be submitted to the REC, and local R&D department for review and approval if appropriate.

Serious breach requirements

A serious breach is one which is likely to effect to a significant degree (a) the safety or physical or mental integrity of the participants of the trial; or b) the scientific value

of the trial. If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) will be notified within 24 hours. It will be the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and, if so, report it to the REC.

All violations will be assessed by the sponsor(s) to ascertain if they meet the criteria for a serious breach. If the sponsor(s) deem the incident to be a violation that does not constitute a serious breach from the protocol when identified, corrective and preventative actions will be taken where appropriate and they will be recorded in file notes, held within the TMF and ISF.

Study record retention

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

End of study

The end of study date was finalised in the protocol after the study commenced; the agreed end of study date is 31/12/2016. The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with good clinical practice guidelines. The clinical study report will be used as the basis for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

DISCUSSION

The data provided by this study will inform the information given to women about reduced fetal movements and their management when they present to maternity services; which has been recurrently identified by Confidential Enquiries into antepartum stillbirths as suboptimal [27 28]. Data from the AFFIRM study will be able to be compared to results from two other active studies which aim to improve mothers awareness and reporting of reduced fetal movements. My Babies Movement (ACTRN 12614000291684) is stepped-wedge cluster trial of a mobile phone application to help women get to know their baby's movements, to be mindful of movements every day and not to wait to report concerns to their maternity care provider. The Mindfetalness study (NCT02865759) is a cluster trial of 39,000 women randomised to routine antenatal care or the Mindfetalness brochure and website.[45] Women participating in the Mindfetalness process will spend 15 minutes each day getting to know their babies movements and will specifically be encouraged to contact their health provider if their perceive reduced fetal movements. This primary

outcome of this study is an Apgar score <7 at 5 minutes; stillbirth and perinatal deaths will be recorded as tertiary endpoints of this study.[45] These large studies will provide much needed robust evidence to determine whether increased maternal awareness of reduced fetal movements combined with a standardised management protocol to identify acute or chronic fetal compromise can reduce stillbirth [33].

PEER REVIEW

This project has been peer reviewed internally, and was externally peer reviewed during the process of securing funding from the Chief Scientist's Office of the Scottish Government, Tommy's and Sands.

FUNDING

The AFFIRM study is investigator initiated and funded by Chief Scientist Office, Scottish Government (CZH/4/882), Tommy's and Sands, the Stillbirth and Neonatal Death Charity. CJW was supported in this work by NHS Lothian via the Edinburgh Clinical Trials Unit. AEPH is supported by a Clinician Scientist fellowship from the National Institute for Health Research (NIHR; CS-2013-009). This protocol presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the support of Perinatal Ireland and Dr Mary Higgins (University College Dublin, National Maternity Hospital, Dublin).

CONTRIBUTIONS

Contributors AEPH, CJW, SJES, CJC, SCB, MRD, SW and JEN were involved in developing the trial design. AEPH, CJW, SJES, AR and JEN were involved in drafting and revision of the article. CJW and AR were involved in drafting the statistical aspects of the protocol. JS provided feedback on behalf of a stakeholder organisation. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS, SW and JEN were involved in preparing the overall study design. AEPH, JEN and MRD prepared education videos for online training. AEPH, SJES, SJS, MG, AH, FMM and JEN facilitated recruitment of sites. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS, SW and JEN will be involved in the collection, management, analysis and interpretation of data and final writing of the trial report.

COMPETING INTERESTS

None declared.

ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
BMI	Body Mass Index
CTG	Cardiotocograph
CTIMP	Clinical Trial of an Investigational Medicinal Product
ECTU	Edinburgh Clinical Trials Unit
FGR	Fetal growth restriction
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Social Care Excellence
NIHR	National Institute for Health Research
NIMATS	Northern Ireland Maternity Statistics database
NRPS	National Perinatal Reporting System
ONS	Office of National Statistics
PSANZ	Perinatal Society of Australia and New Zealand
RCOG	Royal College of Obstetricians and Gynaecologists
R&D	Research and Development
REC	Research Ethics Committee
RFM	Reduced Fetal Movements
SPIMMR	Scottish Perinatal and Infant Mortality and Morbidity Report
TMF	Trial Master File
TSC	Trial Steering Committee
WHO	World Health Organisation

REFERENCES

1. Still-Birth Definition Act Great Britain Curr Law Statut Annot GB, 1992:1.
2. Flenady V, Wojcieszek AM, Middleton P, Ellwood D, Erwich JJ, Coory M, et al. Stillbirths: recall to action in high-income countries. *Lancet* 2016;387(10019):691-702.
3. Flenady V, Koopmans L, Middleton P, Froen JF, Smith GC, Gibbons K, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet* 2011;377(9774):1331-40.
4. Manktelow BM, Smith LK, Seaton SE, Hyman-Taylor P, Kurinczuk JJ, Field DJ, et al. Perinatal Mortality Surveillance Report - UK Perinatal Deaths for births from January to December 2014. Leicester:: The Infant Mortality and Morbidity Group, Department of Health Sciences, University of Leicester., 2016.
5. Lawn JE, Blencowe H, Pattinson R, Cousens S, Kumar R, Ibiebele I, et al. Stillbirths: Where? When? Why? How to make the data count? *Lancet* 2011;377(9775):1448-63.
6. Flenady V, Middleton P, Smith GC, Duke W, Erwich JJ, Khong TY, et al. Stillbirths: the way forward in high-income countries. *Lancet* 2011;377(9778):1703-17.
7. Heazell AE, Whitworth MK, Whitcombe J, Glover SW, Bevan C, Brewin J, et al. Research priorities for stillbirth: process overview and results from UK Stillbirth Priority Setting Partnership. *Ultrasound Obstet Gynecol* 2015;46(6):641-7.
8. Heazell AE, Froen JF. Methods of fetal movement counting and the detection of fetal compromise. *J Obstet Gynaecol* 2008;28(2):147-54.
9. Stacey T, Thompson JM, Mitchell EA, Ekeroma AJ, Zuccollo JM, McCowan LM. The Auckland Stillbirth study, a case-control study exploring modifiable risk factors for third trimester stillbirth: methods and rationale. *The Australian & New Zealand journal of obstetrics & gynaecology* 2011;51(1):3-8.

10. Warland J, O'Brien LM, Heazell AE, Mitchell EA. An international internet survey of the experiences of 1,714 mothers with a late stillbirth: the STARS cohort study. *BMC pregnancy and childbirth* 2015;15:172.

11. Warrander LK, Heazell AE. Identifying placental dysfunction in women with reduced fetal movements can be used to predict patients at increased risk of pregnancy complications. *Medical hypotheses* 2011;76(1):17-20.

12. Vintzileos AM, Fleming AD, Scorza WE, Wolf EJ, Balducci J, Campbell WA, et al. Relationship between fetal biophysical activities and umbilical cord blood gas values. *Am J Obstet Gynecol* 1991;165(3):707-13.

13. Warrander LK, Batra G, Bernatavicius G, Greenwood SL, Dutton P, Jones RL, et al. Maternal perception of reduced fetal movements is associated with altered placental structure and function. *PloS one* 2012;7(4):e34851.

14. Winje BA, Roald B, Kristensen NP, Froen JF. Placental pathology in pregnancies with maternally perceived decreased fetal movement--a population-based nested case-cohort study. *PloS one* 2012;7(6):e39259.

15. Holm Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Froen JF. Maternal characteristics and pregnancy outcomes in women presenting with decreased fetal movements in late pregnancy. *Acta Obstet Gynecol Scand* 2009;88(12):1345-51.

16. Ptacek I, Sebire NJ, Man JA, Brownbill P, Heazell AE. Systematic review of placental pathology reported in association with stillbirth. *Placenta* 2014;35(8):552-62.

17. Healthcare Improvement Scotland. Scottish Perinatal and Infant Mortality and Morbidity Report 2010. Edinburgh: Healthcare Improvement Scotland, 2012.

18. Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. *BMJ (Clinical research ed* 2005;331(7525):1113-7.

19. Saastad E, Winje BA, Stray Pedersen B, Froen JF. Fetal movement counting improved identification of fetal growth restriction and perinatal outcomes--a multi-centre, randomized, controlled trial. *PloS one* 2011;6(12):e28482.

20. Mangesi L, Hofmeyr GJ, Smith V, Smyth RM. Fetal movement counting for assessment of fetal wellbeing. *Cochrane Database Syst Rev* 2015(10):CD004909.

21. Grant A, Elbourne D, Valentin L, Alexander S. Routine formal fetal movement counting and risk of antepartum late death in normally formed singletons. *Lancet* 1989;2(8659):345-9.

22. National Institute for Health and Clinical Excellence. Clinical Guideline 62 - Antenatal care: routine care for the health pregnant woman. London: National Institute for Health and Clinical Excellence, 2008.

23. Sergent F, Lefevre A, Verspyck E, Marpeau L. Decreased fetal movements in the third trimester: what to do? *Gynecol Obstet Fertil* 2005;33(11):861-9.

24. Froen JF, Heazell AE, Tveit JV, Saastad E, Fretts RC, Flenady V. Fetal movement assessment. *Seminars in perinatology* 2008;32(4):243-6.

25. Saastad E, Vangen S, Froen JF. Suboptimal care in stillbirths - a retrospective audit study. *Acta Obstet Gynecol Scand* 2007;86(4):444-50.

26. Froen JF, Arnestad M, Frey K, Vege A, Saugstad OD, Stray-Pedersen B. Risk factors for sudden intrauterine unexplained death: epidemiologic characteristics of singleton cases in Oslo, Norway, 1986-1995. *Am J Obstet Gynecol* 2001;184(4):694-702.

27. Confidential Enquiry into Stillbirths and Deaths in Infancy. 8th Annual Report, 1 January–31 December 1999. London: Maternal and Child Health Research Consortium, 2001.

28. Draper ES, Kurinczuk JJ, Kenyon S, MBRRACE-UK. obo. MBRRACE-UK Perinatal Confidential Enquiry: Term, singleton, normally formed, antepartum

stillbirth. Leicester: The Infant Mortality and Morbidty Studies, Department of Health Sciences, University of Leicester, 2015.

29. Linde A, Pettersson K, Radestad I. Women's Experiences of Fetal Movements before the Confirmation of Fetal Death--Contractions Misinterpreted as Fetal Movement. *Birth* 2015;42(2):189-94.

30. Preston S, Mahomed K, Chadha Y, Flenady V, Gardener G, MacPhail J, et al. Clinical practice guideline for the management of women who report decreased fetal movements. Brisbane,: Australia and New Zealand Stillbirth Alliance, 2010.

31. Royal College Of Obstetricians and Gynaecologists. Management of Reduced Fetal Movements. London: RCOG, 2011.

32. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al. Reduction of late stillbirth with the introduction of fetal movement information and guidelines - a clinical quality improvement. *BMC pregnancy and childbirth* 2009;9:32.

33. Hofmeyr GJ, Novikova N. Management of reported decreased fetal movements for improving pregnancy outcomes. *Cochrane Database Syst Rev* 2012;4:CD009148.

34. Froen JF, Tveit JV, Saastad E, Bordahl PE, Stray-Pedersen B, Heazell AE, et al. Management of decreased fetal movements. *Seminars in perinatology* 2008;32(4):307-11.

35. Dutton PJ, Warrander LK, Roberts SA, Bernatavicius G, Byrd LM, Gaze D, et al. Predictors of poor perinatal outcome following maternal perception of reduced fetal movements--a prospective cohort study. *PloS one* 2012;7(7):e39784.

36. Royal College Of Obstetricians and Gynaecologists. The Investigation And Management Of The Small-For-Gestational-Age Fetus. London: RCOG, 2013.

37. Heazell AE, Green M, Wright C, Flenady V, Froen JF. Midwives' and obstetricians' knowledge and management of women presenting with decreased fetal movements. *Acta Obstet Gynecol Scand* 2008;87(3):331-9.

38. Jokhan S, Whitworth MK, Jones F, Saunders A, Heazell AE. Evaluation of the quality of guidelines for the management of reduced fetal movements in UK maternity units. *BMC pregnancy and childbirth* 2015;15:54.

39. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al. Erratum to: Reduction of late stillbirth with the introduction of fetal movement information and guidelines - a clinical quality improvement. *BMC pregnancy and childbirth* 2010;10:49.

40. Winje BA, Wojcieszek AM, Gonzalez-Angulo LY, Teoh Z, Norman J, Froen JF, et al. Interventions to enhance maternal awareness of decreased fetal movement: a systematic review. *Bjog* 2016;123(6):886-98.

41. Saastad E, Tveit JV, Flenady V, Stray-Pedersen B, Fretts RC, Bordahl PE, et al. Implementation of uniform information on fetal movement in a Norwegian population reduced delayed reporting of decreased fetal movement and stillbirths in primiparous women - a clinical quality improvement. *BMC research notes* 2010;3(1):2.

42. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials* 2007;28(2):182-91.

43. ESRI Health Research and Information Division. Perinatal Statistics Report 2009, 2011.

44. Tominey E. Maternal smoking during pregnancy and early child outcomes. Discussion Paper no. 828. London: Centre for Economic Performance, London School of Economics., 2007.

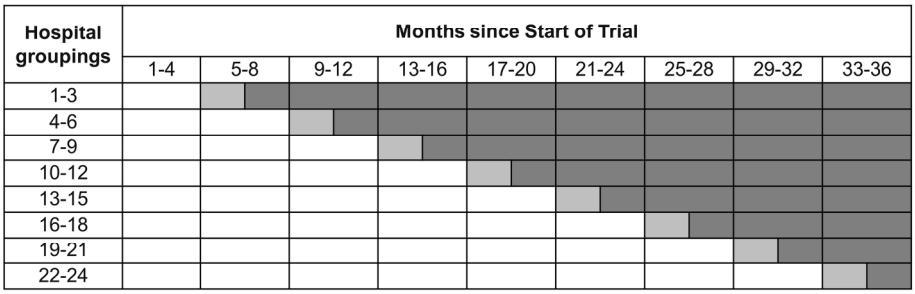
45. Radestad I, Akselsson A, Georgsson S, Lindgren H, Pettersson K, Steineck G. Rationale, study protocol and the cluster randomization process in a controlled trial including 40,000 women investigating the effects of

977 mindfetalness. *Sexual & reproductive healthcare : official journal of the*
978 *Swedish Association of Midwives* 2016;10:56-61.

FIGURE LEGENDS

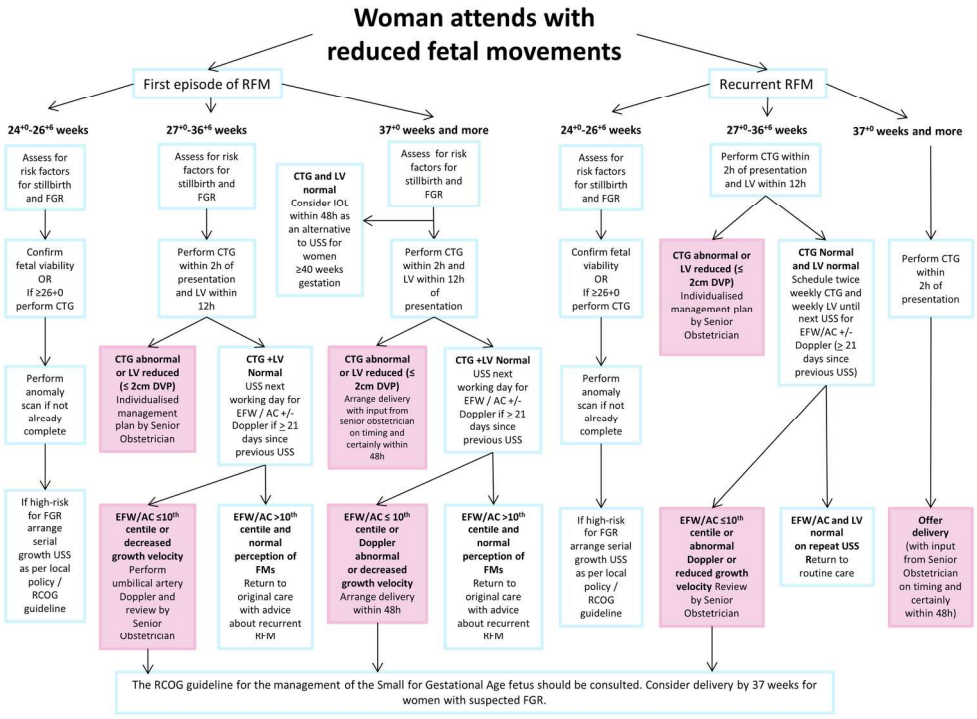
Figure 1 - Stepped wedge design. The shaded areas (both light and dark) indicate periods in which the interventions are being implemented. The lighter areas indicate the “transition” period during which data will not be collected for the control or intervention group. The order in which hospital groupings implement the interventions will be determined via randomization.

Figure 2 – Flow chart for the management of women presenting with reduced fetal movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal movement, USS - ultrasound scan.



Stepped wedge design. The shaded areas (both light and dark) indicate periods in which the interventions are being implemented. The lighter areas indicate the "transition" period during which data will not be collected for the control or intervention group. The order in which hospital groupings implement the interventions will be determined via randomization.

190x142mm (300 x 300 DPI)



Flow chart for the management of women presenting with reduced fetal movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal movement, USS - ultrasound scan.

190x142mm (300 x 300 DPI)

WHO TO CONTACT IF YOU ARE CONCERNED:

(space for sticky with local contact information)

APS Group Scotland
DPPAS33137
Version 3 March 2015

In touch with YOUR BABY

A guide to your baby's movements during pregnancy

AFFIRM

Why are my baby's movements important?

Why are we asking women to get to know their baby's movements?

One of the easiest ways to tell if your baby is healthy is to be aware of how much he or she is moving. Every baby is different and we are asking women to take time to become familiar with their baby's own individual pattern of movements. A reduction or change in **your** baby's movements is what is important.

What can affect my baby's movements?

You are less likely to be aware of your baby's movements when active or busy. Some drugs e.g. strong pain relief or sedatives can get into an unborn baby's circulation and affect the movements. Alcohol and smoking (active and passive smoking) may also affect the baby.

Why are my baby's movements important?

If you notice your baby is moving less than usual, or the pattern of movements has changed, this could be the first sign that your baby may not be well or is not growing properly in the womb. Research has shown that a reduction in the baby's movements may indicate an increased risk of stillbirth. You may hear your midwife or doctor referring to 'reduced fetal movement', or RFM for short.

What are the risks of stillbirth?

Stillbirth affects one in 200 babies after 24 weeks gestation and is one of the most common of the serious complications of pregnancy, affecting the lives of around 4,000 families every year in the UK.

One of the easiest ways to tell if your baby is healthy is to see how much he or she is moving. This booklet tells you what to look out for during your pregnancy.

Every baby is different. It is good to get to know your baby's own movements and the pattern of their sleeping and waking and report to us if you notice a reduction in these movements.

18-24 WEEKS

Most women begin to feel their baby move between 18-24 weeks. At first it may feel like 'bubbles', 'flutterings' or 'like trapped wind'. These are often very short and stop and start. It might take you a little while to be sure what you are feeling. But you will soon get to know the feelings. If this is your second baby, you will know what to look out for and may recognise your baby moving sooner.

Everyone is different when it comes to their movements. There are many reasons you might not feel movements as early as you expect. This includes your body weight, the position of your baby and the location of your placenta. What is important is your baby is growing well. Your midwife will be able to discuss this with you further at your 22 week check.

Try to get to know the times of the day when you are most likely to feel your baby move.

24-36 WEEKS

You will have your own way of describing your baby's own movements. Women often describe their baby's movements as 'rolling', 'kicking', 'pushing', 'jabs', 'elbowing' and 'stretches'.

Between 24-36 weeks you will start to recognise your baby's movements more quickly and become more used to the feeling. It is usually easier to feel your baby's movements when you are lying down, e.g. at night time. It is harder to feel your baby move when you are on your feet and moving around.

Try to get to know the times of the day you are most likely to feel your baby move. This will help you to know if he or she is moving less than normal or if movements have stopped.

Occasionally your baby will get hiccups. These do not count as movements. If you are unsure what you should expect when your baby hiccups, speak to your midwife.

Appendix 3 - Audit of compliance with AFFIRM protocol

Compliance with the AFFIRM management protocol (the management plan for women presenting with reduced fetal movement) will be determined by to means:

A) Telephone / email contact with Principal Investigators at each site to determine which aspects of the AFFIRM protocol have been implemented effectively. This will involve email contact with Principal Investigators to alert them to the request for information, an email detailing the information required, and then a phone call to elicit the information (unless it had already been supplied). Investigators will be asked which of the following elements they had implemented: issuing leaflets to all pregnant women, cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation. “Effective implementation” was defined as the above management for 4/5 of these elements for 80% or more of the time.

B) An audit to determine whether the perception of the site Principal Investigator is supported by review of actual decision making will be performed for the following elements: cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation.

This will be conducted by asking sites to complete an audit of the management of all women presenting with reduced fetal movement over the course of one calendar month. Sites will be asked to complete an audit form for each participant. The audit form template (see below) has been generated by the central

AFFIRM study team; anonymized forms will be analysed centrally. There will not be an attempt to corroborate Principal Investigator perception of the proportion of women who were given leaflets, nor will there be any attempt to incorporate the proportion of staff who had completed the e-learning package into analysis of whether any specific site has implemented the intervention or not.

Compliance with AFFIRM reduced fetal movements protocol, One month data collection AUDIT [Month & Year] Unit name: [Name of Hospital]

If you assess a woman with reduced fetal movements (RFM), please complete the questions below. Do not worry if the woman has been seen in other areas of the hospital by other staff, we would rather have multiple reports for the same woman than miss episodes of RFM.

<table>
<tr><td colspan="5">INSERT Patient Sticker (or WRITE name and CHI /NHS number)</td><td colspan="5">AREA WHERE SEEN (CIRCLE)

Triage / Labour ward / Day Assessment Unit (DAU)

Other (specify area i.e. antenatal ward):_____</td></tr>
<tr><td>Date and time of presentation with reduced fetal movements.</td><td colspan="4">DATE: _____/_____/_____

TIME ____:____ am / pm</td><td>GESTATION AND EDD:</td><td colspan="4">_____ WEEKS _____ DAYS

EDD:_____</td></tr>
<tr><td>Referred by (TICK BOX):</td><td>Self</td><td>Community Midwife</td><td>GP</td><td>ANC</td><td>Triage</td><td>DAU</td><td colspan="3">Other (specify:_____
___</td></tr>
<tr><td>What was the primary reason for attending/phoning? (TICK BOX):</td><td colspan="4">Reduced Fetal Movements</td><td colspan="5">Other (specify: _____</td></tr>
<tr><td>How many times has the woman attended before this visit, with RFM? (TICK BOX):</td><td colspan="2">None – first attendance</td><td colspan="2">Once previously</td><td>Unknown</td><td>Multiple times (please provide the gestation at each presentation i.e. 30+6)</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
<tr><td colspan="6">What was the time interval from the woman first being aware of reduced fetal movements and attending the hospital (in hours)?</td><td colspan="5">HOURS: _____</td></tr>
<tr><td>Has she been given a leaflet “Your baby’s movements in pregnancy”?(TICK BOX):</td><td colspan="2">Yes – she already has one</td><td colspan="3">Yes – I have given one to her today</td><td colspan="2">Locally Created Leaflet Given</td><td colspan="3">NO</td></tr>
<tr><td>Has this woman had a growth USS in this pregnancy? (TICK BOX):</td><td colspan="2">No, she has not had a growth scan</td><td colspan="3">Yes, within the last 3 weeks (date of scan):

DATE: _____/_____/_____</td><td colspan="4">Yes, but more than 3 weeks ago (date of scan):

DATE: _____/_____/_____</td></tr>
</table>

CONTINUATION: NHS/ CHI NUMBER: ……

Are any of the following risk factors for Fetal growth restriction present (CIRCLE all that apply)?							
Age ≥40 or ≤16	Smoker ≥20cpd	Known or suspected growth restriction	Congenital anomaly	Raised BP (essential hypertension, pre-eclampsia or pregnancy induced hypertension)	Previous pre-eclampsia	Diabetes or gestational diabetes	Previous FGR or stillbirth

What investigations were conducted during this episode of reduced fetal movement?			
Please record below the date and time that these investigations were completed or indicate if not performed.			**Please provide the results (CIRCLE):**
CTG	Not performed ☐	DATE: ___/___/_____ TIME: _____:_____ am/pm ***Computerised CTG***: YES / NO **(CIRCLE)**	Normal / Suspicious / Pathological
Liquor volume assessment on scan	Not performed ☐	DATE: ___/___/_____ TIME: _____:_____ am/pm	Normal / Reduced / Increased
Growth scan	Not performed ☐	DATE: ___/___/_____ TIME: _____:_____ am/pm	Normal / EFW < 10th centile/ AC < 10th centile / EFW and AC < 10th centile
Umbilical Artery Doppler	Not performed ☐	DATE: ___/___/_____ TIME: _____:_____ am/pm	Normal/.> 95th centile/absent EDF/reversed EDF
MCA Doppler	Not performed ☐	DATE: ___/___/_____ TIME: _____:_____ am/pm	Normal/<5th centile

DELIVERY METHOD (If available)			
Was the woman offered induction of labour	YES / NO **(CIRCLE)** **IF Yes,** please provide date, time and method of the induction:	DATE: _____/ _____/ _____ TIME: _____:_____ am/pm	
Was the woman offered elective caesarean section as a result of the reduced fetal movement?	YES / NO **(CIRCLE)** **IF Yes,** please provide date, time and reason:	DATE: _____/ _____/ _____ TIME: _____:_____ am/pm	Please provide the reason for the elective Caesarean section:

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____Page 1____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____Page 4____
	2b	All items from the World Health Organization Trial Registration Data Set	_Included throughout protocol_
Protocol version	3	Date and version identifier	_____Page 4 ____
Funding	4	Sources and types of financial, material, and other support	____Page 28__
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_Names and affiliations Page 1 and 2; Contributions Page 28_
	5b	Name and contact information for the trial sponsor	____Page 24___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_Not applicable__

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____Page 24___
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__Pages 5-11___
	6b	Explanation for choice of comparators	__Pages 8-9____
Objectives	7	Specific objectives or hypotheses	__Pages 11-12__
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	__Pages 13- 14 and Figure 1 ____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__Pages 13 & 16_
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__Pages 14-15___
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__Pages 17-18 and Figure 2___
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	__Not applicable in AFFIRM trial__
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__Pages 17-18___
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__Not applicable_

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__Pages 12-13___
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Randomisation by site explained in Figure 1 and Pages 13-14___
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__Pages21-22 __
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__Page 22 _____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__Page 17 _____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__Page 17 _____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__Page 17 ____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__Page 17 ____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_ Not applicable in AFFIRM study___

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__Pages 18-21___
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__Not applicable_
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__Pages 19-20__
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__Pages 22-23___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__Page 23_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__Pages 22-23__

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_DMC not required, explanation Pg 24___
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__Pages 18, 25-26__
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__Page 24_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__Page 13_____

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___Page 25_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___Page 25_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___Page 25_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__Not applicable_
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__Page 20_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__Page 29_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__Page 27_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__Page 24_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__Page 27____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__Page 28 ____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Not applicable_

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Not Applicable__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_Not Applicable__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014813.R2
Article Type:	Protocol
Date Submitted by the Author:	07-Feb-2017
Complete List of Authors:	Heazell, Alexander; University of Manchester, Maternal and Fetal Health Research Centre Weir, Christopher; University of Edinburgh, MRC Hub for Trials Methodology Research; Edinburgh Clinical Trials Unit Stock, Sarah; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health,; School of Women's and Infants' Health, University of Western Australia, Crawley WA 6009. (FMM) Calderwood, Catherine; The Scottish Government St Andrew's House, EH1 3DG., Chief Medical Officer for Scotland, CunninghamBurley, Sarah; University of Edinbrugh, Public Health Sciences Froen, Frederik; Nasjonalt folkehelseinstitutt, Division of Epidemiology Geary, Michael; Rotunda Hospital, Parnell Square Hunter, Alyson; Royal Maternity Hospital, Grosvenor Road, BT12 6BB McAuliffe, Fionnuala; University College Dublin, Murdoch, Edile; Royal Infirmary of Edinburgh, NHS Lothian, EH16 4SA., Department of Neonatology Rodriguez, Aryelly; University of Edinburgh, (ECTU) Edinburgh Clinical Trials Unit Ross-Davie, Mary; NHS Education for Scotland, 3rd Floor, Hanover Buildings, 66 Rose Street, EH2 2NN. Scott, Janet; Sands, Victoria Charity Centre, Suite GF2 Ground Floor, 11 Belgrave Road, SW1V 1RB. Whyte, Sonia; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health, Norman, Jane; , Queen's Medical Research Institute, EH16 4TJ
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Research methods
Keywords:	Reduced Fetal Movements, Perinatal Mortality, Stillbirth, Neonatal Death, Fetal Growth Restriction

Study Protocol

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

Alexander E P HEAZELL,[1,2] alexander.heazell@manchester.ac.uk

Christopher J WEIR, [3,4] christopher.weir@ed.ac.uk

Sarah J E STOCK,[5 6] sarah.stock@ed.ac.uk

Catherine J CALDERWOOD,[7] catherine.calderwood@scotland.gsi.gov.uk

Sarah CUNNINGHAM-BURLEY,[4] sarah.c.burley@ed.ac.uk

J Frederik FROEN,[8] frederik.froen@fhi.no

Michael GEARY,[9] mppgeary@gmail.com

Alyson HUNTER,[10] alyson.hunter@belfasttrust.hscni.net

Fionnuala M MCAULIFFE,[11] fionnuala.mcauliffe@ucd.ie

Edile MURDOCH,[12] edile.murdoch@nhslothian.scot.nhs.uk

Aryelly RODRIGUEZ,[3,4] aryelly.rodriguez@ed.ac.uk

Mary ROSS-DAVIE,[13] mary.ross-davie@nes.scot.nhs.uk

Janet SCOTT [14] janet.scott@uk-sands.org

Sonia WHYTE [5] sonia.whyte@ed.ac.uk

Jane E NORMAN.[5] jane.norman@ed.ac.uk

1. Maternal and Fetal Health Research Centre, Institute of Human Development, University of Manchester. 2. St. Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, M13 9WL. 3. Edinburgh Clinical Trials Unit, Edinburgh, UK 4. Centre for

Population Health Sciences, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG. 5. Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health, Queen's Medical Research Institute, Edinburgh, EH16 4TJ.6. School of Women's and Infants' Health, University of Western Australia, Crawley WA 6009. (FMM) 7. Chief Medical Officer for Scotland, The Scottish Government St Andrew's House Edinburgh EH1 3DG. 8. Department of International Public Health, Norwegian Institute of Public Health, PB 4404 Nydalen, N-0403 Oslo, Norway, 9. Rotunda Hospital, Parnell Square, Dublin 1, Ireland. 10. Centre for Fetal Medicine, Royal Maternity Hospital, Grosvenor Road, Belfast, BT12 6BB 11. UCD Obstetrics & Gynaecology, School of Medicine, University College Dublin, Ireland. National Maternity Hospital, Dublin, Ireland. 12. Department of Neonatology, Royal Infirmary of Edinburgh, NHS Lothian, Edinburgh, EH16 4SA. 13. NHS Education for Scotland, 3rd Floor, Hanover Buildings, 66 Rose Street, Edinburgh EH2 2NN. 14. Sands, Victoria Charity Centre, Suite GF2 Ground Floor, 11 Belgrave Road, London, SW1V 1RB.

Abstract

Background - In 2013, the stillbirth rate in the UK was 4.2 per 1,000 live births, ranking 24th out of 49 high-income countries, with an annual rate of reduction of only 1.4% per year. The majority of stillbirths occur in normally formed infants, with (retrospective) evidence of placental insufficiency the commonest clinical finding. Maternal perception of reduced fetal movements (RFM) is associated with placental insufficiency and increased risk of subsequent stillbirth.

This study will test the hypothesis that the introduction of a package of care to increase women's awareness of the need for prompt reporting of RFM and standardised management to identify fetal compromise with timely delivery in confirmed cases, will reduce the rate of stillbirth. Following the introduction of a similar intervention in Norway the odds of stillbirth fell by 30%, but the efficacy of this intervention (and possible adverse effects and implications for service delivery) have not been tested in a randomised trial.

Methods - We describe a stepped wedge cluster trial design, in which participating hospitals in the UK and Ireland will be randomized to the timing of introduction of the care package. Outcomes (including the primary outcome of stillbirth) will be derived from detailed routinely collected maternity data, allowing us to robustly test our hypothesis. The degree of implementation of the intervention will be assessed in each site. A nested qualitative study will examine the acceptability of the intervention to women and health care providers and identify process issues including barriers to implementation.

Discussion - The data provided by this study will inform the management of women with RFM; which has been recurrently identified as suboptimal in cases of stillbirth. This will provide robust evidence to determine whether increased maternal awareness of RFM combined with a standardised management protocol to identify acute or chronic fetal compromise can reduce stillbirth.

Trial Registration

www.clinicaltrials.gov NCT01777022

Version

Protocol Version 4.2, 19th December 2016

Keywords

Reduced Fetal Movements; Perinatal Mortality; Stillbirth; Neonatal Death; Fetal Growth Restriction.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This trial directly addresses the need for studies of the information given to women regarding fetal movements and the subsequent management of reduced fetal movements identified by Confidential Enquiries into Antepartum Stillbirths, Systematic Reviews and the Stillbirth Priority Setting Partnership.
- A stepped-wedge cluster trial design in combination with routinely collected maternity data allows the trial to be adequately powered to detect a difference in stillbirth as a primary outcome.
- The pragmatic nature of the study represents the potential impact of the introduction of such standardised care into clinical practice.
- The nested qualitative study will provide information regarding the acceptability of the intervention and identify barriers and facilitators to its adoption.
- The lack of information on resource use before and throughout the study period limits the ability to understand the consequences of the intervention on maternity unit workload.

INTRODUCTION

Stillbirth

Stillbirth, defined in the UK as a baby with no signs of life after 24 weeks of completed pregnancy [1], remains the major cause of perinatal mortality in high-income environments, with a recent series of papers in the Lancet on stillbirth issue calling for renewed action in this area [2]. There is no single "cause" of stillbirth, and a significant proportion of stillbirths remain unexplained, but fetal growth restriction, maternal hypertension and low socioeconomic status are amongst the identifiable risk factors [3]. The concept that more can be done to reduce stillbirth in the UK and Ireland is supported by data showing a marked variation in rates between resource rich countries, when similar definitions of stillbirth are used [2]. Notably, the UK has a higher rate than comparable resource rich countries such as Germany, Netherlands, New Zealand and Norway with rates in the UK some 50% greater than those of the Netherlands. Disappointingly, the annual rate of reduction in stillbirth from 2000 to 2014 in the UK was only 1.4% compared to 6.8% in the Netherlands and 2.8% in New Zealand [2]. Rates of stillbirth in Scotland (3.7 per 1,000 births in 2014) and Ireland, at (4.4 per 1,000 livebirths in 2013) are similar to rates in England and Wales at 4.2 per 1,000 livebirths (England and Wales, 2014) [4]. The reduction of avoidable harm for women and babies is viewed as a major priority for Government and its agencies throughout the UK and Ireland. Consequently, several initiatives have been developed by national governments in the UK and Ireland including the Scottish Government Stillbirth Working Group, NHS England Saving Babies' Lives Care Bundle and the Welsh Assembly 1000 Lives Plus strategy. These strategies have identified the need for better evidence to guide efforts to prevent stillbirths.

Using a robust priority setting strategy [5] the Lancet Stillbirth's series steering committee identified issues around detection and management of reduced fetal movements (RFM) amongst the top ten key research questions on prevention and

management of stillbirth [6]. This was confirmed in the UK-based Stillbirth Priority Setting partnership involving over 1,700 parents and professionals which identified two relevant issues among the highest ranked research questions regarding stillbirth: i) which investigations identify a fetus at risk of stillbirth after a mother believes she has experienced reduced fetal movements? and ii) would more accessible evidence-based information on signs and symptoms of stillbirth risk, designed to empower women to raise concerns with healthcare professionals, reduce the incidence of stillbirth? [7] Thus, RFM has been identified as a highly-relevant area of study by parents, professionals and researchers.

Reduced Fetal Movements, Stillbirth and Placental Insufficiency

There is a clear association between maternal perception of RFM and late stillbirth dating back over four decades [8]. In a recent series of 2,000 women, the adjusted OR (95% CI) of late stillbirth in women with RFM (compared with controls) was 2.37 (1.29-4.35) [9]. One international study of 1,714 women who experienced a stillbirth found that 30% had noted significant RFM prior to the diagnosis of stillbirth [10]. Although the mechanisms have not been fully delineated, it is likely that RFM and stillbirth are linked by a common pathology, that of placental dysfunction [11]. There is good evidence linking placental dysfunction and RFM. Compared to controls with an active fetus women who have fewer fetal movements on ultrasound scan immediately prior to caesarean section are more likely to have umbilical cord gas measurements indicative of acidaemia, hypoxaemia, and hypercapnia [12]. Women delivering within one week of an episode of RFM show differences in placental structure and function which are reminiscent of those seen in fetal growth restriction (FGR) and stillbirth [13 14]. Additionally, the odds of fetal growth restriction (FGR, defined as being at less than the 10th centile for gestation adjusted birthweight) were greater in women with RFM compared with controls (adjusted OR 1.6, 95% CI 1.1–2.2 [15]). Taken together these

data are strong evidence that placental dysfunction is associated with RFM, and a causative pathway seems likely.

The evidence linking placental dysfunction and stillbirth is even stronger; a systematic review of placental pathology in stillbirths described abnormalities in up to 65% of cases [10]. Amongst the 291 stillbirths in Scotland in 2010, 137 (47%) had evidence of placental dysfunction [16]. Given that the placenta was examined in only 80% of stillbirths, the true prevalence of placental dysfunction is likely to be higher. In addition, between 20%-40% of stillborn babies are reported to have FGR, as defined by a birthweight less than the 10th centile [17]. Additionally, the Lancet report notes that "placental pathologies accounted for one in four deaths across all gestational ages, and were contributory or causal in more than half of cases" [6]. Given that stillbirth is strongly related to placental dysfunction, and RFM is a "biomarker" of placental dysfunction then better management of women presenting with RFM focussing on the detection of placental dysfunction might reduce the risk of stillbirth.

Formal Fetal Movement Counting

Although prenatal detection of FGR is improved by fetal movement counting [18], a systematic review [19], and a large and influential cluster randomised trial (which dominates the systematic review) showed that routine fetal movement counting using the count to ten charts had no effect on perinatal mortality [20]. Thus, the National Institute for Health and Social Care Excellence (NICE) recommended that "Routine formal fetal movement counting should not be offered" [21]. Importantly, the large cluster randomised trial tested a specific alarm limit for RFM, but did not recommend a specific management strategy for women who did present with RFM. There were two important observations from this study, firstly that in both groups the perinatal mortality rate was lower than contemporary or subsequent periods in the UK and secondly that more women in the fetal movement counting arm came in with a live baby who subsequently died compared with the control arm (19 vs 11), suggesting

that one reason the strategy failed to reduce perinatal mortality was inadequate investigation and management of those presenting with RFM [20].

Optimal strategy for determining RFM to prompt maternal presentation to the maternity service

Maternal concern about RFM is a common reason to contact maternity services with between 6-15% of women presenting during the third trimester.[22 23] Nevertheless, delays in reporting RFM to maternity care providers may increase the risk of adverse outcome.[24 25] The lack of good-quality information given to women about fetal movements has been highlighted as an example of suboptimal care in Confidential Enquiries into Antepartum Stillbirth.[26 27] Qualitative studies suggest that women frequently perceive RFM two days prior to the diagnosis of fetal death, and in some cases contractions were misinterpreted as fetal movements.[28] Therefore, giving information to women regarding fetal movements and when they should be concerned about RFM is a key component of an intervention to reduce stillbirth.

However, giving clear information about RFM can be challenging as there is no uniform threshold of fetal movements below which perinatal morbidity increases [23], and no evidence that a specific threshold performs better than maternal perception of reduced fetal movements alone [8]. Current guidelines from the RCOG and PSANZ [29 30], informed by a large Norwegian study [31] suggest that it is maternal *perception* of decreased fetal movement which is important. Therefore, information for pregnant women in this study (shown in Supplementary File 1) described the importance of fetal movements, the need to get to know normal fetal activity, how fetal movements change in late pregnancy and who to contact if the mother perceives RFM. The educational package aimed to ensure that these messages were reinforced by staff behaviour at antenatal contacts.

Optimal strategy for investigation and management of women presenting with RFM.

A recent systematic review found there are no proven strategies for the investigation and management of women presenting with RFM [32]. Cardiotocography (CTG) is routinely used to ascertain fetal wellbeing, and it is the cornerstone of the RCOG guideline [30]. However, data from Norway, suggests that ultrasound assessment of fetal size is often the most helpful investigation, performing well on both an absolute basis, and compared with other interventions [33]. In a series of over 3,000 women with RFM, ultrasound (including measurement of fetal biometry and liquor volume) was found to be useful in detecting abnormalities in 11.6% of scans. In 71% of women in whom an abnormality was found, ultrasound was the only technique that detected an abnormality. Additionally, 85% of abnormalities detected by ultrasound, were important in informing the clinical management of the woman [33]. These data are supported by a smaller UK study which found that abnormalities detected on CTG or ultrasound scan were most strongly associated with adverse outcome in women with RFM, with identification of abnormal estimated fetal growth centile on scan being the test most highly predictive of poor outcome [34]. Perhaps this is not surprising, given the strong association between RFM and placental dysfunction and the central importance of ultrasound in the identification and management of small for gestational age babies [35]. Given these data, it is concerning that a survey of clinicians in Scotland showed that fewer than 5% would routinely refer women with RFM for ultrasound examination (unpublished data from June 2012), and a survey of 223 UK midwives and obstetricians described that 17.9% of respondents would perform an ultrasound scan [36]. These views of clinicians may reflect the variable quality of local guidelines, which are frequently not based on national recommendations, even those for which there is strong evidence [37].The variation in information given to women and subsequent management of RFM has been highlighted as sources of suboptimal care in two confidential enquiries into antepartum stillbirth [26 27]. Therefore, we believe that current investigation of women presenting with RFM is inadequate, hence using the best available evidence, we have drafted what we consider to be a robust evaluation

protocol for investigation of women with RFM.

Potentially efficacy of a package of intervention for RFM

Supportive data for the package of interventions used in this study (information for women and standardised management protocol) comes from a large observational "clinical quality improvement study" in Norway which found a significant fall in rates of stillbirth (from 3.0/1,000 to 2.0/1,000 [OR 0.67 95% CI 0.48–0.93]) after the introduction of an intervention package consisting of written information for women about awareness of RFM combined with consensus guidelines for health professionals about their management [31]. Although this study was not randomised, and therefore constitutes only level II-3 evidence, it has informed recommendations from the Royal College of Obstetricians and Gynaecologists (RCOG) and Perinatal Society of Australia and New Zealand (PSANZ) that "women should be advised to be aware of their baby's individual pattern of movements and that if they are concerned about a reduction in or cessation of fetal movements …..they should contact their maternity unit" [29 30].Following initial publication of the Norwegian study, a re-analysis was required as discrepancies between stillbirth rates in the study and the Medical Birth Registry of Norway were identified. This reanalysis found the reduction in stillbirth rates was of borderline statistical significance (OR 0.72, 95% CI 0.50-1.03). The authors concluded that further studies were needed to determine whether this approach was associated with a reduction in stillbirth [38].

Importantly, in the Norwegian study, there was no increase in the proportion of women who presented with RFM when rates were compared before and after the intervention [31]. However, women with RFM presented significantly earlier to hospital than they had hitherto, potentially allowing time for intervention to reduce perinatal mortality. These data suggest that a package of interventions encouraging women with RFM to present early to hospital, combined with a structured approach to their management might reduce rates of stillbirth without contributing to a large increase in admissions antenatally.

Potential harms of a package of care around increased awareness and optimised management of RFM

Any clinical intervention which aims to improve outcomes also has the ability to do harm. Thus, it is essential that the intervention proposed is rigorously evaluated using the gold standard technique of a randomised trial, rather than being introduced as a service development. When the study began, there was a small window of opportunity to do this, as the enthusiasm to improve current management of RFM is such that routine introduction of the package of care is unlikely to be delayed much further than the current scheduled end date of this study. Possible harms of a package of care consisting of a management plan for identification and delivery of the "at risk" fetus, together with strategies for increasing pregnant women's awareness of the need to report early include increased maternal anxiety and increased intervention (including hospital admission, induction of labour and Caesarean section) which itself is associated with pregnancy related complications. The available evidence is reassuring on some of these issues. A systematic review of 23 publications from 16 studies found three studies involving 2,030 women addressing maternal concern and an additional three studies involving 1,468 women investigating maternal-fetal attachment. These demonstrated no evidence of increased maternal anxiety and results regarding maternal-fetal attachment were discordant.[39] In the Norwegian service development study, the package of care increased rates of follow up of women, but there was no increase in admissions overall, admissions for induction or admissions for emergency caesarean section [31] – again, whilst reassuring these outcomes require formal evaluation in a randomised and relevant setting to the UK and Republic of Ireland. The final possible harm of the package is around increased resource use, and the opportunity cost of focussing on RFM rather than other potential methods to prevent stillbirth.

RATIONALE

The aim of this study is to test the hypothesis that a package of interventions consisting of strategies for increasing pregnant women's awareness of the need to report early when they perceive a reduction in fetal movements, followed with a management plan for identification and delivery of the "at risk" fetus in such women, will reduce rates of stillbirth.

STUDY OBJECTIVES

Primary Objective

The primary objective is to answer the research question 'Does the introduction of a protocol for detection and management of decreased fetal movements reduce rates of stillbirth?' The secondary objectives are to answer the following research questions:

- What is the effect of the intervention on rates of caesarean section and induction of labour?
- What is the effect of the intervention on rates of admission to the neonatal intensive care unit?
- What is the effect of the intervention on the proportion of women with FGR remaining undelivered by 40 weeks gestation?
- What is the acceptability of such a package of care to pregnant women and their health care providers?
- What other process outcomes are influenced by the intervention, such as health care provider/patient interactions?

ENDPOINTS

Primary Outcome

The primary endpoint is stillbirth (antepartum and intrapartum). We will use the UK definition of stillbirth which is "a baby delivered without signs of life after 23^{+6} weeks" [4]. Where gestation is uncertain we will include all babies with a birth weight of 500g or more.

Secondary Endpoints

Other measures of perinatal mortality including:

- Stillbirth at 37 weeks gestation and above
- Stillbirth at 28 weeks gestation and above (WHO definition of stillbirth)
- Stillbirth at 22 weeks gestation and above (international stillbirth alliance definition)
- Stillbirths amongst normally formed infants of 22 weeks gestation and above, 24 weeks gestation and above, 28 weeks gestation and above and 37 weeks gestation and above.
- Perinatal mortality (defined as stillbirth at 24 weeks gestation and above and deaths in the first seven days of life)
- Rates of caesarean section
- Rates of induction of labour (for any indication)
- Rates of elective delivery (induction of labour and caesarean section prior to the onset of labour) overall
- Rates of induction of labour at 39 weeks gestation or later
- Mean gestation at induction of labour
- Rates of admission to the neonatal unit (and their reasons)

- Rates of admission to the neonatal unit for more than 48 hours
- Rates of admission to the neonatal unit for term babies (those born at 37 weeks 0 days or greater)
- Proportion of infants with fetal growth restriction (less than the 5th centile, customised for gender) remaining undelivered at or after 40 weeks gestation
- Birthweight centile (according to the Intergrowth birthweight centile calculator at https://intergrowth21.tghn.org)
- Rates of spontaneous vaginal delivery

Other secondary outcomes are the baby parameters:

- Gestation at birth
- Proportion of babies born preterm (<37 weeks gestation)
- Gender of the baby
- Birthweight of the baby
- Apgar score at 5 minutes
- Proportion of babies with 5 minute Apgar score < 7
- Proportion of babies with 5 minute Apgar score < 4
- Resuscitation required at birth

We will also collect the following data: maternal age, maternity unit of delivery, birthweight, gestation of delivery, parity, gestation, sex, smoking (current and ever), maternal body mass index (BMI), number of babies (one or more), ethnicity (to allow a customised birthweight centile to be generated), method of delivery, deprivation category (where available) and other neonatal variables including Apgar score and encephalopathy. Adjustment will be made for the following variables: (maternal age,

maternity unit of delivery, parity, smoking status, maternal BMI, number of babies [one or more] and ethnicity)

STUDY DESIGN

This is a multicentre, stepped wedge cluster randomised trial of a package of care consisting of a management plan for identification and delivery of the 'at risk' fetus, together with strategies for increasing pregnant women's awareness of the need to report RFM early. The trial developed from a planned quality improvement project proposed by the Scottish Government to reduce stillbirths. This was planned to emphasise the importance of fetal movement monitoring and was to be rolled out to all NHS maternity units in Scotland. However, prior to this change it was agreed that the roll out could be performed in such a way as to allow the assessment of the effect of the intervention, the stepped-wedge design would be the natural choice in this circumstance.

The study will take place in participating hospitals in the UK and Ireland (a complete list is available http://www.crh.ed.ac.uk/affirm/randomised-hospitals/). A nested qualitative study will examine the acceptability of the intervention to patients and health care providers and identify process issues (barriers to implementation). Clinical audit (detailed in Appendix 3) conducted after the change in practice will be used to determine the effect of interventions on process outcomes (e.g. number of women presenting with reduced fetal movements, interval between perceiving reduced fetal movements and presentation to hospital, number of ultrasound scans, number of admissions for induction of labour). A diagram indicating randomisation of hospital groupings in the stepped wedge design is shown in Figure 1.

The interventions will be introduced over a 32 month period. Data will be collected over a 36 month period. Data in the 'active phase' after introduction of the

intervention will be compared to data in the 'control phase' – the period during which usual care processes in study sites are followed from study start to the time of introduction of the intervention. Given that it will take individual units some time (a) to effect change in management in their unit from time of introduction of the intervention and (b) that it will take some time for this change in practice to impact on clinical outcomes, we plan a "washout" period of two months after the introduction of the intervention during which data will not be included in either group for analysis (Figure 1). Data will be collected four months after the last birth, a further two months has been included for data analysis, giving a total study duration of 42 months.

STUDY POPULATION

Number of participants

Participants will be those delivering at all the sites over the study period (36 months). All eligible women will be recruited to the cluster randomised controlled trial. Based on previous delivery numbers, after accounting for a washout period of two months (and assuming no withdrawals or losses to follow up) this is estimated to be a total of around 143,140 women per annum. A subset of around 30 participating women and 30 midwives, sonographers and obstetricians will be recruited to the nested qualitative study, which is based in the Scottish sites.

Inclusion criteria

We will include all women delivering at one of the participating maternity units for the duration of the study. Women who have been seen at any of the maternity units but who deliver at home will not be included. The duration of the study will be 42 months from the start of the trial (01/02/2014). For practical reasons, participants for the nested qualitative study will be recruited from the participating units in Scotland.

Exclusion criteria

We will exclude women as follows:

- Women for whom data on delivery outcomes is still unavailable four months after the date of delivery
- Women delivering in the "washout" period in each unit.

Members of the trial management group and participants who do not speak/understand English will be excluded from participating in the nested qualitative study.

Identifying participants

Women will be identified from those whose data is included in routine data returns from each unit. Potential participants for the nested qualitative study will be identified from those attending antenatal clinics in participating hospitals, and/or local staff.

Consenting participants

The main study is a stepped wedge cluster randomised trial of a package of care which would be introduced in many of the participating units regardless of whether the trial was on-going or not and the trial uses only routinely collected data on participants. The ethics committee indicated that formal individual patient consent is not necessary for the main trial. Participants in the nested qualitative study will be asked for individual consent.

Screening for eligibility

As participants are not directly recruited we will not perform any specific screening tests for this aspect of this project. Participants for the nested qualitative study will be: (i) Pregnant women attending hospitals who are participating in the main trial in Scotland. Purposive sampling will ensure that the final sample set includes women who have and who have not experienced RFM, both before and after the introduction of the intervention; (ii) Hospital staff (including midwives, ultrasonographers and

obstetricians/radiologists) working in participating hospitals in Scotland. There will be no specific screening tests for eligibility for the nested qualitative study, except that women who have experienced a stillbirth in the index pregnancy will not be approached.

Ineligible and non-recruited participants

Potential participants for the nested qualitative study who are not approached or who decline will have no specific interventions / procedures.

Withdrawal of Study Participants

The nature of a cluster randomised study is such that it is not possible for the participant to withdraw from the "cluster" unless she changes maternity unit part way through her pregnancy. We plan to collect routinely recorded anonymised data; patients have the right to opt out of having their data used – if this happens their data would be excluded from the study database (e.g. under the Confidentiality and Security advisory Group Report 2002 and the Data Protection Act (1998) requirements for fair processing of data). Participants in the nested qualitative study who wish to withdraw will be allowed to do so. Their data will be retained and used, unless they additionally indicate that they wish to withdraw their data.

RANDOMISATION

Randomisation Procedures

This is a cluster-randomised, stepped-wedge design trial wherein maternity units rather than individual patients are randomised. All units will implement the fetal movement monitoring intervention at some point during the trial; the random element is the time point at which this will occur, the so-called "step" of the stepped-wedge design. Participating maternity units will be blinded to their randomly allocated time point until the time this is required to be revealed to enable the necessary training in the implementation of the intervention to be delivered. Primary and secondary

outcomes of the trial will be gathered in a blinded manner via routinely collected data sources.

Maternity units which are in close proximity to each other will be grouped for the purposes of randomisation. This will assist with the feasibility of delivering the training for and implementation of the intervention. Furthermore, this local synchronisation of the intervention implementation will minimise the chances of contamination (introduction of the intervention prematurely) from maternity units which have already implemented the intervention to those not yet randomised.

The order in which the groups of maternity units step in to implement the intervention will be determined by computer generated random numbers from a uniform distribution. The randomisation list will be held by the Edinburgh Clinical Trials Unit (ECTU). The identities of the research team staff whose roles in the trial require them to be unblinded to randomisation codes will be recorded in the trial master file (TMF).

Treatment Allocation

Participating sites will be randomised to different schedules for implementing the intervention. All units will be providing conventional treatment at baseline according to local practice – this is the treatment established before the study starts. Sites will be randomised to “active” treatment in turn as described above. Active treatment will consist of a package of care consisting of a management plan for identification and delivery of the ‘at risk’ fetus, together with strategies for increasing pregnant women’s awareness of the need to report RFM early. The recommended management plan for identification and delivery of the “at risk” fetus is shown in Figure 2. Practice change in the active units will be achieved by: (i) written/email information to all clinicians (doctors, midwives and ultrasonographers) in each unit about the study protocol and amendment of the local protocol for Reduced Fetal Movements (RFM) to that of the study protocol; (ii) a short web-based training package taking approximately one hour to complete for all clinicians in each centre and (iii) training /information sessions to

run in each unit and (iv) posters in each unit to describe the practice change. Strategies for encouraging clinicians to increase pregnant women's awareness of fetal movement will include all the above and also a fetal movement leaflet for pregnant women (shown in Supplementary Information 1). The Norwegian quality improvement study showed inconclusive results regarding the effect of the intervention in non-European women.[40] To attempt to address this, the AFFIRM information leaflet was available in 12 languages including: Arabic, Bengali, English, Hindi, Hungarian, Latvian, Lithuanian, Mandarin, Polish, Russian and Urdu. Furthermore, by including staff education which highlighted the need to ask women about fetal movements in routine antenatal consultations as many women as possible should have received information about what to do if they perceive RFM.

Once units have begun active treatment it is not anticipated that they will return to conventional treatment. We will conduct an audit of women presenting with reduced fetal movements and assess the proportion of staff completing the online training to assess the extent to which sites have followed the intervention plan. Units will be informed about treatment allocation as near as possible to the implementation of the "active" treatment. For practical purposes, we anticipate that each unit will need around three months' notice before the "active" treatment is introduced, hence units will be informed of the timing of their treatment allocation (step) three months before the active treatment is due to start. The treatment allocation will not be administered blind and there are no restrictions on concomitant care or other interventions during the study, hence there is no need for emergency unblinding and there are no stopping rules for the study.

DATA COLLECTION

For the main trial, data will be accessed from the information routinely collected during the clinical management of the patient. For consistency, we will normally only

include data items which become available within four months after the delivery date in question, although we may seek advice from the independently-chaired trial steering committee (TSC) about exceptions as they arise. Different data sources will be used for different regions of the study: (i) In Scotland the source data will be SMR2 and the Scottish Birth record, (ii) In Ireland the source data will be the National Perinatal Reporting System (NRPS http://www.esri.ie/health_information/nprs), (iii) In Northern Ireland, the source data will be the Northern Ireland maternity Statistics database (NIMATS), (iv) In England and Wales, the source data will be the ONS, or other relevant body. Data will be collected retrospectively on an annual basis from all sources. We will assume that data unavailable four months after the woman delivered is likely to be unobtainable (but see note in Study Design section above). Thus, data on the first year of the study will be collected at month 16; data on the second year will be collected at month 28 etc.

Data are routinely collected. A formal request for data access will be made at the start of the study. This will require (i) in Scotland – Privacy Advisory Committee approval and a formal approach to NHS Scotland Information Services Division (ISD) (ii) in Ireland a formal approach to NRPS (iii) NIMATS in Northern Ireland (iv) in England and Wales a formal approach will be made to the relevant bodies.

Data will then be sent to the electronic Data Research and Innovation Service (eDRIS) National Safe Haven (NHS National Services Scotland) by secure file transfer protocol (or other similar) for storage and subsequent analysis within a secure project area (dedicated to the AFFIRM study). Further information on the National Safe Haven is available at http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven. Briefly, the National Safe Haven is located on a secure server, in which trusted and authorised researchers can analyse individual level data while maintaining the utmost

confidentiality. It is anticipated that all study analysis will be done within the Safe Haven, using one of the available statistical packages (e.g. R, SPSS).

Identifiers on Scottish data within the National Safe Haven are concealed from researchers. Data from outwith Scotland will be anonymised before submission to the National Safe Haven. We propose that data submitted to the National Safe Haven will be "anonymised" by the data provider. However, we propose that the anonymisation link will be retained at the source so that it will be possible to re-link data retrospectively. The rationale for retaining the ability of local data guardians to re-link data is because it is important to retain the possibility of identifying individual patients retrospectively. Examples include: (i) It is possible that some additional important data may be available at a late stage on individual participants – e.g. in the scenario where the woman or baby had a major adverse event and spent a long time in hospital before discharge or death and (ii) Although our protocol and outcome analysis does not require identifiable data, we believe this will be a 'once in a lifetime" study, and that subsequent secondary analyses could yield important information for patients and for policy makers. If retrospective identification is not possible, this will limit further analysis. One likely example of future analyses is to determine the effect of the intervention on different causes of stillbirth. This is outwith the scope of the current protocol, but could be done relatively straightforwardly, by linking nationally recorded information on "cause" of stillbirth to our study database. We anticipate that such additional analyses would require additional ethics approval, but without a process by which to re-link data, it will not be possible to perform such subsequent analyses.

All Investigators and study site staff involved with this study will comply with the requirements of the Data Protection Act 1998 (or equivalent for those outwith the UK) with regard to the collection, storage, processing and disclosure of personal

information and will uphold the Act's core principles. Published results will not contain any personal data that could allow identification of an individual participant.

In addition to the data recorded above, all sites will be asked to provide a copy of their guidelines around (i) maternal awareness of RFM and (ii) management of women presenting with RFM. Copies of guidelines will be sought by the study office (a) at the start of the study (b) immediately before initiation of the intervention in each specific unit and (c) six months after initiation of the intervention in each specific unit.

For the nested qualitative study, we will perform interviews of healthcare workers and a small nested cohort of pregnant women about their experiences of fetal movement and of this intervention. We shall ensure a diversity of age and include nulliparous and multiparous women (n=30 in total). Ten interviews will be conducted with each of the following groups of health care providers: obstetricians, midwives and sonographers/radiologists. The interviews will take a semi-structured format (sensitising and piloting interviews will be conducted prior to the commencement of the trial and in the first month of the nested qualitative study). This format will ensure the same categories of data will be obtained from each participant but also allow individual responses to be fully explored.

STATISTICS AND DATA ANALYSIS

Sample size calculation

The sample size is the number of women delivering in hospitals participating in the study. This was initially planned to include sites in Scotland, totalling around 58,000 deliveries per year with 16 consultant led maternity units, 20 smaller units each delivering less than 350 babies per year, and seven units delivering less than five births per year. The units involved in Perinatal Ireland (an all-Ireland research consortium across 7 academic sites in Ireland currently funded by the Health

Research Board, Ireland) have 50,000 births per year with seven large sites. Combining one or two of the smaller units and one larger unit into a single "hospital group" for each local area could provide 24 hospital "groups" – the details of hospital groupings will be reviewed and finalised immediately prior to randomisation. In total, 36 sites expressed interest in participating in the study, although 2 were unable to participate in the study and withdrew before randomisation. In total, 34 units were randomised, these were situated throughout the UK and Ireland (10 in England, 4 in Ireland, 15 in Scotland and 5 in Wales) with 143,140 births per annum.

We calculated statistical power using the methodology for stepped wedge designs proposed in Hussey and Hughes (2007).[41] First, we analysed stillbirth event data from the Scottish Perinatal and Infant Mortality and Morbidity Report (SPIMMR) covering years 2005-2010 [16] to determine estimates of between- and within-unit variability in stillbirth rate. Analysis was by generalized linear mixed model for binary outcomes. The power calculation, as per equations (#7) and (#8) in [41] assumed: significance level 5%; analysis by generalized linear mixed model; deliveries equally distributed across hospital groupings; baseline stillbirth rate 0.438% [16]; cluster coefficient of variation 0.333.

Finally, the statistical power depends on the number of groups in which the intervention is implemented at each stage of the stepped wedge design and the duration of recruitment at each "step". Our study design proposes sequential introduction of the intervention into three hospital groups at a time in eight steps at four month intervals. This would give 92.4% power to detect a 30% risk reduction under the intervention and 80.7% power to detect a 25% reduction. A 30% risk reduction was seen in the Norwegian study; the anticipated effect sizes of 25% and 30% relative reduction take into account that the intervention will not have the power to reduce all stillbirths, since 20% of stillbirths in Ireland [42] and 15% in Scotland [16] are associated with congenital anomaly.

The power actually achieved in the study will be slightly lower, as deliveries during the two month "transition" period following implementation of the intervention in a site will not be included in the analysis. The effect of this was explored using the Stata function steppedwedge,[43] which showed the statistical power would become 88.2% (30% risk reduction) and 74.6% (25% risk reduction). It is anticipated that unavailability of data and women asking to withdraw their data will be less than 1%.

Proposed analyses

For the binary primary and secondary outcomes, data will be analysed by generalized linear mixed model with a random effect for hospital and fixed effects for the intervention implementation and study time period. A site by intervention interaction random effect will be included in the model and retained if it explains an important proportion of the variability in outcomes. The primary analysis of data will be on an intention to treat basis (the design of the trial means it is not possible to determine individual patient /caregiver compliance with the intervention). An "on treatment" variable will be calculated for which women will be grouped as active or control according to when the intervention was actually implemented in their site, instead of when the site was randomised to implement the intervention. The primary outcome will be reanalysed in two sensitivity analyses. Firstly, we will perform the analysis according to the actual timing of the implementation of the intervention rather than the randomised timing of the intervention using the "on treatment" classification. Secondly, we will perform the analysis in the subgroup of sites who were deemed to have implemented the intervention effectively according to the perception of the Principal Investigator at each site. The accuracy of this perception will be confirmed with the findings of a site audit (details in Appendix 3). There will be no attempt to correlate the impact of the intervention according to the results of the site audit.

There are no planned imputations for missing data. However, if the missing data rate for smoking status during pregnancy is relatively high an imputation technique will be devised. The imputation method will be informed using smoking history at booking and age at delivery [44]. A pre-specified subgroup analysis will be performed for babies with and without congenital anomalies, and will be implemented by testing for an intervention by congenital anomaly interaction added to the generalised linear mixed model described above. No formal interim analyses for efficacy or safety will be performed. A full statistical analysis plan will be finalised prior to locking of the study database.

Qualitative Data

For the nested qualitative study, the data will be audio recorded and transcribed. The data will be coded thematically and an analytical framework developed to make sense of patient experience of fetal movement and the intervention and also health care providers' perspectives and experiences. NVivo will be utilised to support the analysis.

Process outcomes

The process outcomes being assessed by the (rates of induction of labour, number of women presenting with reduced fetal movements, interval between perceiving fetal movements and presenting to hospital) will be analysed using the same methods as for the main trial, with the exception of the continuous outcome (interval between perceiving fetal movements and presenting to hospital) which will be analysed using a normal linear mixed model.

ADVERSE EVENTS

This is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) so adverse events will not be formally reported. Stillbirth and other measures of fetal and

maternal morbidity are outcomes of the study. The purpose of the intervention is to reduce such adverse events. Therefore, due to the low risks for this trial, a separate DMC is not required and the Trial Steering Committee (TSC) will cover any responsibilities normally allocated to a DMC. If considered necessary, the TSC may review unblinded data for the study, including morbidity and mortality indices. No other adverse event reporting will be undertaken.

TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

The trial will be coordinated by a Project Management Group, consisting of the grant holders and the Trial Manager. The Chief Investigator (JN) will lead the project management group. The Trial Manager will oversee the study and will be accountable to the Chief Investigator. A TSC will be established to oversee the conduct and progress of the trial. The terms of reference and a draft template for reporting will be ratified in one of the early meetings of the TSC.

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the co-sponsors (ACCORD: Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian, Sponsor contact: ray.french@ed.ac.uk), research ethics committee (REC) review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

Study monitoring and audit

The sponsor determined that as no individual participants were recruited to the intervention, and it was not a clinical trial of an investigational medicinal product (CTIMP) no formal monitoring and audit was required.

Good Clinical Practice and Ethical Conduct

The study will be conducted in accordance with the principles of the research governance framework operational and good clinical practice in the relevant country. A favorable ethical opinion has been obtained from the Scotland A REC (Reference 13/SS/0001) and local research and development approval has been obtained prior to commencement of the study.

Local study investigator(s) will be appointed to each site (or for small units, groups of sites). S/he will be responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments.

STUDY CONDUCT RESPONSIBILITIES

Protocol amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, will be reviewed and approved by the Chief Investigator and Sponsor. Amendments to the protocol will be submitted in writing to the appropriate REC and local Research and Development (R&D) department for approval prior to participants being enrolled into an amended protocol.

Protocol violations and deviations

Investigators will not implement any deviation from the protocol without agreement from the Chief Investigator and appropriate REC and R&D department approval except where necessary to eliminate an immediate hazard to trial participants. In the event that an Investigator needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded. If this necessitates a subsequent protocol amendment, this will be submitted to the REC, and local R&D department for review and approval if appropriate.

Serious breach requirements

A serious breach is one which is likely to effect to a significant degree (a) the safety or physical or mental integrity of the participants of the trial; or b) the scientific value of the trial. If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) will be notified within 24 hours. It will be the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and, if so, report it to the REC.

All violations will be assessed by the sponsor(s) to ascertain if they meet the criteria for a serious breach. If the sponsor(s) deem the incident to be a violation that does not constitute a serious breach from the protocol when identified, corrective and preventative actions will be taken where appropriate and they will be recorded in file notes, held within the TMF and ISF.

Study record retention

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

End of study

The end of study date was finalised in the protocol after the study commenced; the agreed end of study date is 31/12/2016. The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with good clinical practice guidelines. The clinical study report will be used as the basis for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

DISCUSSION

The data provided by this study will inform the information given to women about reduced fetal movements and their management when they present to maternity

services; which has been recurrently identified by Confidential Enquiries into antepartum stillbirths as suboptimal [26 27]. Data from the AFFIRM study will be able to be compared to results from two other active studies which aim to improve mothers awareness and reporting of reduced fetal movements. My Babies Movement (ACTRN 12614000291684) is stepped-wedge cluster trial of a mobile phone application to help women get to know their baby's movements, to be mindful of movements every day and not to wait to report concerns to their maternity care provider. The Mindfetalness study (NCT02865759) is a cluster trial of 39,000 women randomised to routine antenatal care or the Mindfetalness brochure and website.[45] Women participating in the Mindfetalness process will spend 15 minutes each day getting to know their babies movements and will specifically be encouraged to contact their health provider if their perceive reduced fetal movements. This primary outcome of this study is an Apgar score <7 at 5 minutes; stillbirth and perinatal deaths will be recorded as tertiary endpoints of this study.[45] These large studies will provide much needed robust evidence to determine whether increased maternal awareness of reduced fetal movements combined with a standardised management protocol to identify acute or chronic fetal compromise can reduce stillbirth [32].

PEER REVIEW

This project has been peer reviewed internally, and was externally peer reviewed during the process of securing funding from the Chief Scientist's Office of the Scottish Government, Tommy's and Sands.

FUNDING

The AFFIRM study is investigator initiated and funded by Chief Scientist Office, Scottish Government (CZH/4/882), Tommy's and Sands, the Stillbirth and Neonatal Death Charity. CJW was supported in this work by NHS Lothian via the Edinburgh

Clinical Trials Unit. AEPH is supported by a Clinician Scientist fellowship from the National Institute for Health Research (NIHR; CS-2013-009). This protocol presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the support of Perinatal Ireland and Dr Mary Higgins (University College Dublin, National Maternity Hospital, Dublin).

CONTRIBUTIONS

Contributors AEPH, CJW, SJES, CJC, SCB, MRD, SW and JEN were involved in developing the trial design. AEPH, CJW, SJES, AR and JEN were involved in drafting and revision of the article. CJW and AR were involved in drafting the statistical aspects of the protocol. JS provided feedback on behalf of a stakeholder organisation. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS, SW and JEN were involved in preparing the overall study design. AEPH, JEN and MRD prepared education videos for online training. AEPH, SJES, SJS, MG, AH, FMM and JEN facilitated recruitment of sites. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS, SW and JEN will be involved in the collection, management, analysis and interpretation of data and final writing of the trial report.

COMPETING INTERESTS

None declared.

ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
BMI	Body Mass Index
CTG	Cardiotocograph
CTIMP	Clinical Trial of an Investigational Medicinal Product
ECTU	Edinburgh Clinical Trials Unit
FGR	Fetal growth restriction
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Social Care Excellence
NIHR	National Institute for Health Research
NIMATS	Northern Ireland Maternity Statistics database
NRPS	National Perinatal Reporting System
ONS	Office of National Statistics
PSANZ	Perinatal Society of Australia and New Zealand
RCOG	Royal College of Obstetricians and Gynaecologists
R&D	Research and Development
REC	Research Ethics Committee
RFM	Reduced Fetal Movements
SPIMMR	Scottish Perinatal and Infant Mortality and Morbidity Report
TMF	Trial Master File
TSC	Trial Steering Committee
WHO	World Health Organisation

REFERENCES

1. Curtis L, Burns A. Unit Costs of Health and Social Care 2015 Canterbury: Personal Social Services Research Unit, The University of Kent, 2015.
2. Warland J, O'Brien LM, Heazell AE, Mitchell EA. An international internet survey of the experiences of 1,714 mothers with a late stillbirth: the STARS cohort study. *BMC pregnancy and childbirth* 2015;15:172.
3. Flenady V, Koopmans L, Middleton P, Froen JF, Smith GC, Gibbons K, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet* 2011;377(9774):1331-40.
4. Manktelow BM, Smith LK, Seaton SE, Hyman-Taylor P, Kurinczuk JJ, Field DJ, et al. Perinatal Mortality Surveillance Report - UK Perinatal Deaths for births from January to December 2014. Leicester:: The Infant Mortality and Morbidity Group, Department of Health Sciences, University of Leicester., 2016.
5. Sadovsky E, Polishuk WZ. Fetal movements in utero: nature, assessment, prognostic value, timing of delivery. *Obstet Gynecol* 1977;50(1):49-55.
6. Flenady V, Middleton P, Smith GC, Duke W, Erwich JJ, Khong TY, et al. Stillbirths: the way forward in high-income countries. *Lancet* 2011;377(9778):1703-17.
7. Heazell AE, Whitworth MK, Whitcombe J, Glover SW, Bevan C, Brewin J, et al. Research priorities for stillbirth: process overview and results from UK Stillbirth Priority Setting Partnership. *Ultrasound Obstet Gynecol* 2015;46(6):641-7.
8. Heazell AE, Froen JF. Methods of fetal movement counting and the detection of fetal compromise. *J Obstet Gynaecol* 2008;28(2):147-54.
9. Stacey T, Thompson JM, Mitchell EA, Ekeroma AJ, Zuccollo JM, McCowan LM. The Auckland Stillbirth study, a case-control study exploring modifiable risk factors for third trimester stillbirth: methods and rationale. *The Australian & New Zealand journal of obstetrics & gynaecology* 2011;51(1):3-8.

10. Ptacek I, Sebire NJ, Man JA, Brownbill P, Heazell AE. Systematic review of placental pathology reported in association with stillbirth. *Placenta* 2014;35(8):552-62.

11. Warrander LK, Heazell AE. Identifying placental dysfunction in women with reduced fetal movements can be used to predict patients at increased risk of pregnancy complications. *Medical hypotheses* 2011;76(1):17-20.

12. Vintzileos AM, Fleming AD, Scorza WE, Wolf EJ, Balducci J, Campbell WA, et al. Relationship between fetal biophysical activities and umbilical cord blood gas values. *Am J Obstet Gynecol* 1991;165(3):707-13.

13. Warrander LK, Batra G, Bernatavicius G, Greenwood SL, Dutton P, Jones RL, et al. Maternal perception of reduced fetal movements is associated with altered placental structure and function. *PloS one* 2012;7(4):e34851.

14. Winje BA, Roald B, Kristensen NP, Froen JF. Placental pathology in pregnancies with maternally perceived decreased fetal movement--a population-based nested case-cohort study. *PloS one* 2012;7(6):e39259.

15. Holm Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Froen JF. Maternal characteristics and pregnancy outcomes in women presenting with decreased fetal movements in late pregnancy. *Acta Obstet Gynecol Scand* 2009;88(12):1345-51.

16. Healthcare Improvement Scotland. Scottish Perinatal and Infant Mortality and Morbidity Report 2010. Edinburgh: Healthcare Improvement Scotland, 2012.

17. Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. *BMJ (Clinical research ed* 2005;331(7525):1113-7.

18. Saastad E, Winje BA, Stray Pedersen B, Froen JF. Fetal movement counting improved identification of fetal growth restriction and perinatal outcomes--a multi-centre, randomized, controlled trial. *PloS one* 2011;6(12):e28482.

19. Mangesi L, Hofmeyr GJ, Smith V, Smyth RM. Fetal movement counting for assessment of fetal wellbeing. *Cochrane Database Syst Rev* 2015(10):CD004909.

20. Grant A, Elbourne D, Valentin L, Alexander S. Routine formal fetal movement counting and risk of antepartum late death in normally formed singletons. *Lancet* 1989;2(8659):345-9.

21. National Institute for Health and Clinical Excellence. Clinical Guideline 62 - Antenatal care: routine care for the health pregnant woman. London: National Institute for Health and Clinical Excellence, 2008.

22. Sergent F, Lefevre A, Verspyck E, Marpeau L. Decreased fetal movements in the third trimester: what to do? *Gynecol Obstet Fertil* 2005;33(11):861-9.

23. Froen JF, Heazell AE, Tveit JV, Saastad E, Fretts RC, Flenady V. Fetal movement assessment. *Seminars in perinatology* 2008;32(4):243-6.

24. Saastad E, Vangen S, Froen JF. Suboptimal care in stillbirths - a retrospective audit study. *Acta Obstet Gynecol Scand* 2007;86(4):444-50.

25. Froen JF, Arnestad M, Frey K, Vege A, Saugstad OD, Stray-Pedersen B. Risk factors for sudden intrauterine unexplained death: epidemiologic characteristics of singleton cases in Oslo, Norway, 1986-1995. *Am J Obstet Gynecol* 2001;184(4):694-702.

26. Confidential Enquiry into Stillbirths and Deaths in Infancy. 8th Annual Report, 1 January–31 December 1999. London: Maternal and Child Health Research Consortium, 2001.

27. Manktelow BM, Smith LK, Evans TA, Hyman-Taylor P, Kurinczuk JJ, Field DJ, et al. Perinatal Mortality Surveillance Report - UK Perinatal Deaths for births from January to December 2013. . Leicester:: The Infant Mortality and Morbidity Group, Department of Health Sciences, University of Leicester., 2015.

28. Linde A, Pettersson K, Radestad I. Women's Experiences of Fetal Movements before the Confirmation of Fetal Death--Contractions Misinterpreted as Fetal Movement. *Birth* 2015;42(2):189-94.

29. Preston S, Mahomed K, Chadha Y, Flenady V, Gardener G, MacPhail J, et al. Clinical practice guideline for the management of women who report decreased fetal movements. Brisbane,: Australia and New Zealand Stillbirth Alliance, 2010.

30. Royal College Of Obstetricians and Gynaecologists. Management of Reduced Fetal Movements. London: RCOG, 2011.

31. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al. Reduction of late stillbirth with the introduction of fetal movement information and guidelines - a clinical quality improvement. *BMC pregnancy and childbirth* 2009;9:32.

32. Hofmeyr GJ, Novikova N. Management of reported decreased fetal movements for improving pregnancy outcomes. *Cochrane Database Syst Rev* 2012;4:CD009148.

33. Froen JF, Tveit JV, Saastad E, Bordahl PE, Stray-Pedersen B, Heazell AE, et al. Management of decreased fetal movements. *Seminars in perinatology* 2008;32(4):307-11.

34. Dutton PJ, Warrander LK, Roberts SA, Bernatavicius G, Byrd LM, Gaze D, et al. Predictors of poor perinatal outcome following maternal perception of reduced fetal movements--a prospective cohort study. *PloS one* 2012;7(7):e39784.

35. Royal College Of Obstetricians and Gynaecologists. The Investigation And Management Of The Small-For-Gestational-Age Fetus. London: RCOG, 2013.

36. Heazell AE, Green M, Wright C, Flenady V, Froen JF. Midwives' and obstetricians' knowledge and management of women presenting with decreased fetal movements. *Acta Obstet Gynecol Scand* 2008;87(3):331-9.

37. NHS England. Saving Babies' Lives - A care bundle for reducing stillbirth. Leeds: Acute Care Policy Unit, 2015.

38. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al. Correction: Reduction of late stillbirth with the introduction of fetal movement information and guidelines - a clinical quality improvement. *BMC pregnancy and childbirth* 2010;10:49.

39. Winje BA, Wojcieszek AM, Gonzalez-Angulo LY, Teoh Z, Norman J, Froen JF, et al. Interventions to enhance maternal awareness of decreased fetal movement: a systematic review. *Bjog* 2016;123(6):886-98.

40. Mitchell ML. Fetal brain to liver weight ratio as a measure of intrauterine growth retardation: analysis of 182 stillborn autopsies. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc* 2001;14(1):14-9.

41. Barbaux S, Erwich JJ, Favaron PO, Gil S, Gallot D, Golos TG, et al. IFPA meeting 2014 workshop report: Animal models to study pregnancy pathologies; new approaches to study human placental exposure to xenobiotics; biomarkers of pregnancy pathologies; placental genetics and epigenetics; the placenta and stillbirth and fetal growth restriction. *Placenta* 2015;36 Suppl 1:S5-10.

42. Coleman SJ, Gerza L, Jones CJ, Sibley CP, Aplin JD, Heazell AE. Syncytial nuclear aggregates in normal placenta show increased nuclear condensation, but apoptosis and cytoskeletal redistribution are uncommon. *Placenta* 2013;34(5):449-55.

43. Hemming K, Girling A. A menu-driven facility for power and detectable-difference calculations in stepped-wedge cluster-randomized trials. *The Stata Journal* 2014;14:363-80.

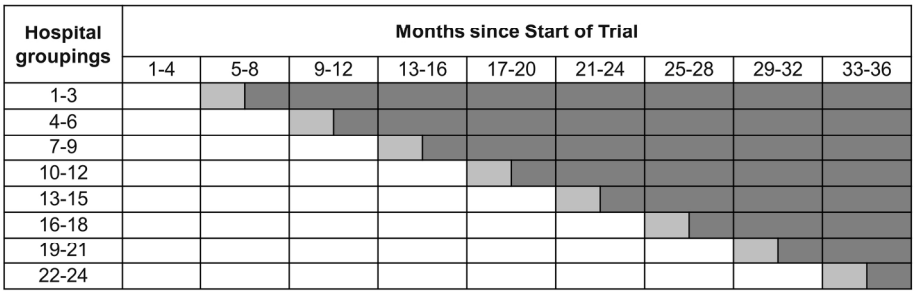
44. Jokhan S, Whitworth MK, Jones F, Saunders A, Heazell AE. Evaluation of the quality of guidelines for the management of reduced fetal movements in UK maternity units. *BMC pregnancy and childbirth* 2015;15:54.

45. Radestad I, Akselsson A, Georgsson S, Lindgren H, Pettersson K, Steineck G. Rationale, study protocol and the cluster randomization process in a controlled trial including 40,000 women investigating the effects of mindfetalness. *Sexual & reproductive healthcare : official journal of the Swedish Association of Midwives* 2016;10:56-61.

FIGURE LEGENDS

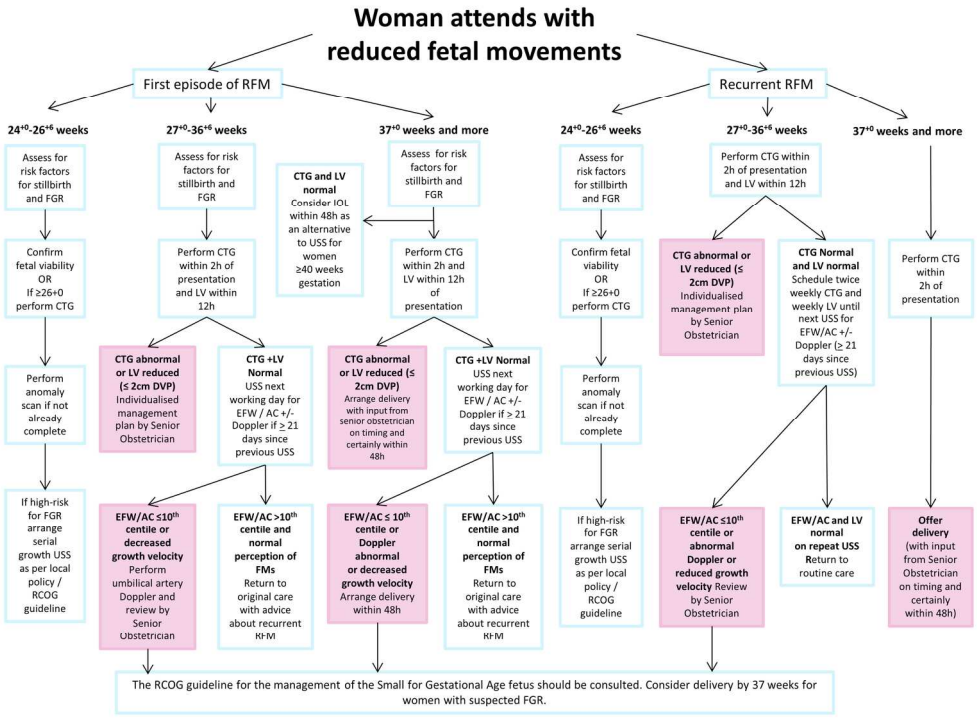
Figure 1 - Stepped wedge design. The shaded areas (both light and dark) indicate periods in which the interventions are being implemented. The lighter areas indicate the “transition” period during which data will not be collected for the control or intervention group. The order in which hospital groupings implement the interventions will be determined via randomization.

Figure 2 – Flow chart for the management of women presenting with reduced fetal movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal movement, USS - ultrasound scan.



Stepped wedge design. The shaded areas (both light and dark) indicate periods in which the interventions are being implemented. The lighter areas indicate the "transition" period during which data will not be collected for the control or intervention group. The order in which hospital groupings implement the interventions will be determined via randomization.

190x142mm (300 x 300 DPI)



Flow chart for the management of women presenting with reduced fetal movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal movement, USS - ultrasound scan.

190x142mm (300 x 300 DPI)

WHO TO CONTACT IF YOU ARE CONCERNED:

(space for sticky with local contact information)

APS Group Scotland
DPPAS33137
Version 3 March 2015

In touch with YOUR BABY

A guide to your baby's movements during pregnancy

Why are my baby's movements important?

Why are we asking women to get to know their baby's movements?

One of the easiest ways to tell if your baby is healthy is to be aware of how much he or she is moving. Every baby is different and we are asking women to take time to become familiar with their baby's own individual pattern of movements. A reduction or change in **your** baby's movements is what is important.

What can affect my baby's movements?

You are less likely to be aware of your baby's movements when active or busy. Some drugs e.g. strong pain relief or sedatives can get into an unborn baby's circulation and affect the movements. Alcohol and smoking (active and passive smoking) may also affect the baby.

Why are my baby's movements important?

If you notice your baby is moving less than usual, or the pattern of movements has changed, this could be the first sign that your baby may not be well or is not growing properly in the womb. Research has shown that a reduction in the baby's movements may indicate an increased risk of stillbirth. You may hear your midwife or doctor referring to 'reduced fetal movement', or RFM for short.

What are the risks of stillbirth?

Stillbirth affects one in 200 babies after 24 weeks gestation and is one of the most common of the serious complications of pregnancy, affecting the lives of around 4,000 families every year in the UK.

One of the easiest ways to tell if your baby is healthy is to see how much he or she is moving. This booklet tells you what to look out for during your pregnancy.

Every baby is different. It is good to get to know your baby's own movements and the pattern of their sleeping and waking and report to us if you notice a reduction in these movements.

18-24 WEEKS

Most women begin to feel their baby move between 18-24 weeks. At first it may feel like 'bubbles', 'flutterings' or 'like trapped wind'. These are often very short and stop and start. It might take you a little while to be sure what you are feeling. But you will soon get to know the feelings. If this is your second baby, you will know what to look out for and may recognise your baby moving sooner.

Everyone is different when it comes to their movements. There are many reasons you might not feel movements as early as you expect. This includes your body weight, the position of your baby and the location of your placenta. What is important is your baby is growing well. Your midwife will be able to discuss this with you further at your 22 week check.

Try to get to know the times of the day when you are most likely to feel your baby move.

24-36 WEEKS

You will have your own way of describing your baby's own movements. Women often describe their baby's movements as 'rolling', 'kicking', 'pushing', 'jabs', 'elbowing' and 'stretches'.

Between 24-36 weeks you will start to recognise your baby's movements more quickly and become more used to the feeling. It is usually easier to feel your baby's movements when you are lying down, e.g. at night time. It is harder to feel your baby move when you are on your feet and moving around.

Try to get to know the times of the day you are most likely to feel your baby move. This will help you to know if he or she is moving less than normal or if movements have stopped.

Occasionally your baby will get hiccups. These do not count as movements. If you are unsure what you should expect when your baby hiccups, speak to your midwife.

Appendix 2 - Audit of compliance with AFFIRM protocol

Compliance with the AFFIRM management protocol (the management plan for women presenting with reduced fetal movement) will be determined by to means:

A) Telephone / email contact with Principal Investigators at each site to determine which aspects of the AFFIRM protocol have been implemented effectively. This will involve email contact with Principal Investigators to alert them to the request for information, an email detailing the information required, and then a phone call to elicit the information (unless it had already been supplied). Investigators will be asked which of the following elements they had implemented: issuing leaflets to all pregnant women, cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation. "Effective implementation" was defined as the above management for 4/5 of these elements for 80% or more of the time.

B) An audit to determine whether the perception of the site Principal Investigator is supported by review of actual decision making will be performed for the following elements: cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation.

This will be conducted by asking sites to complete an audit of the management of all women presenting with reduced fetal movement over the course of one calendar month. Sites will be asked to complete an audit form for each participant. The audit form template (see below) has been generated by the central

AFFIRM study team; anonymized forms will be analysed centrally. There will not be an attempt to corroborate Principal Investigator perception of the proportion of women who were given leaflets, nor will there be any attempt to incorporate the proportion of staff who had completed the e-learning package into analysis of whether any specific site has implemented the intervention or not.

Compliance with AFFIRM reduced fetal movements protocol, One month data collection AUDIT [Month & Year] Unit name: [Name of Hospital]

If you assess a woman with reduced fetal movements (RFM), please complete the questions below. Do not worry if the woman has been seen in other areas of the hospital by other staff, we would rather have multiple reports for the same woman than miss episodes of RFM.

<table>
<tr><td colspan="5">INSERT Patient Sticker (or WRITE name and CHI /NHS number)</td><td colspan="5">AREA WHERE SEEN (CIRCLE)

Triage / Labour ward / Day Assessment Unit (DAU)

Other (specify area i.e. antenatal ward):_____</td></tr>
<tr><td>Date and time of presentation with reduced fetal movements.</td><td colspan="4">DATE: _____/_____/_____

TIME ____:____ am / pm</td><td>GESTATION AND EDD:</td><td colspan="4">_____ WEEKS _____ DAYS

EDD:_____</td></tr>
<tr><td>Referred by (TICK BOX):</td><td>Self</td><td>Community Midwife</td><td>GP</td><td>ANC</td><td>Triage</td><td>DAU</td><td colspan="3">Other (specify:_____ ___</td></tr>
<tr><td>What was the primary reason for attending/phoning? (TICK BOX):</td><td colspan="4">Reduced Fetal Movements</td><td colspan="5">Other (specify: _____</td></tr>
<tr><td>How many times has the woman attended before this visit, with RFM? (TICK BOX):</td><td colspan="2">None – first attendance</td><td colspan="2">Once previously</td><td>Unknown</td><td>Multiple times (please provide the gestation at each presentation i.e. 30+6)</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
<tr><td colspan="6">What was the time interval from the woman first being aware of reduced fetal movements and attending the hospital (in hours)?</td><td colspan="5">HOURS: _____</td></tr>
<tr><td>Has she been given a leaflet “Your baby’s movements in pregnancy”?(TICK BOX):</td><td colspan="3">Yes – she already has one</td><td colspan="2">Yes – I have given one to her today</td><td colspan="2">Locally Created Leaflet Given</td><td colspan="3">NO</td></tr>
<tr><td>Has this woman had a growth USS in this pregnancy? (TICK BOX):</td><td colspan="2">No, she has not had a growth scan</td><td colspan="3">Yes, within the last 3 weeks (date of scan):

DATE: _____/_____/_____</td><td colspan="4">Yes, but more than 3 weeks ago (date of scan):

DATE: _____/_____/_____</td></tr>
</table>

CONTINUATION: NHS/ CHI NUMBER: ……

Are any of the following risk factors for Fetal growth restriction present (CIRCLE all that apply)?							
Age ≥40 or ≤16	Smoker ≥20cpd	Known or suspected growth restriction	Congenital anomaly	Raised BP (essential hypertension, pre-eclampsia or pregnancy induced hypertension)	Previous pre-eclampsia	Diabetes or gestational diabetes	Previous FGR or stillbirth

What investigations were conducted during this episode of reduced fetal movement?			
Please record below the date and time that these investigations were completed or indicate if not performed.			**Please provide the results (CIRCLE):**
CTG	Not performed ☐	DATE: ___/___/_____ TIME: _____:_____ am/pm *Computerised CTG*: YES / NO (CIRCLE)	Normal / Suspicious / Pathological
Liquor volume assessment on scan	Not performed ☐	DATE: ___/___/_____ TIME: _____:_____ am/pm	Normal / Reduced / Increased
Growth scan	Not performed ☐	DATE: ___/___/_____ TIME: _____:_____ am/pm	Normal / EFW < 10th centile/ AC < 10th centile / EFW and AC < 10th centile
Umbilical Artery Doppler	Not performed ☐	DATE: ___/___/_____ TIME: _____:_____ am/pm	Normal/.> 95th centile/absent EDF/reversed EDF
MCA Doppler	Not performed ☐	DATE: ___/___/_____ TIME: _____:_____ am/pm	Normal/<5th centile

DELIVERY METHOD (If available)			
Was the woman offered induction of labour	YES / NO (CIRCLE) **IF Yes,** please provide date, time and method of the induction:	DATE: _____/ _____/ _____ TIME: _____:_____ am/pm	
Was the woman offered elective caesarean section as a result of the reduced fetal movement?	YES / NO (CIRCLE) **IF Yes,** please provide date, time and reason:	DATE: _____/ _____/ _____ TIME: _____:_____ am/pm	Please provide the reason for the elective Caesarean section:

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____Page 1____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____Page 4____
	2b	All items from the World Health Organization Trial Registration Data Set	_Included throughout protocol_
Protocol version	3	Date and version identifier	_____Page 4 ____
Funding	4	Sources and types of financial, material, and other support	____Page 28__
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_Names and affiliations Page 1 and 2; Contributions Page 28_
	5b	Name and contact information for the trial sponsor	____Page 24___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_Not applicable__

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____Page 24___
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__Pages 5-11___
	6b	Explanation for choice of comparators	__Pages 8-9____
Objectives	7	Specific objectives or hypotheses	__Pages 11-12__
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	__Pages 13- 14 and Figure 1 ____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__Pages 13 & 16_
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__Pages 14-15___
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__Pages 17-18 and Figure 2___
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	__Not applicable in AFFIRM trial__
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__Pages 17-18___
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__Not applicable_

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__Pages 12-13___
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Randomisation by site explained in Figure 1 and Pages 13-14___
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__Pages21-22 __
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__Page 22 _____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__Page 17 _____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__Page 17 _____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__Page 17 ____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__Page 17 ____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_ Not applicable in AFFIRM study___

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__Pages 18-21___
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__Not applicable_
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__Pages 19-20__
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__Pages 22-23___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__Page 23_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__Pages 22-23__

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_DMC not required, explanation Pg 24___
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__Pages 18, 25-26__
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__Page 24_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__Page 13_____

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___Page 25_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___Page 25_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___Page 25_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__Not applicable_
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__Page 20_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__Page 29_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__Page 27_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__Page 24_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__Page 27____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__Page 28 ____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Not applicable_

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Not Applicable__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_Not Applicable__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014813.R3
Article Type:	Protocol
Date Submitted by the Author:	02-Mar-2017
Complete List of Authors:	Heazell, Alexander; University of Manchester, Maternal and Fetal Health Research Centre Weir, Christopher; University of Edinburgh, MRC Hub for Trials Methodology Research; Edinburgh Clinical Trials Unit Stock, Sarah; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health,; School of Women's and Infants' Health, University of Western Australia, Crawley WA 6009. (FMM) Calderwood, Catherine; The Scottish Government St Andrew's House, EH1 3DG., Chief Medical Officer for Scotland, CunninghamBurley, Sarah; University of Edinbrugh, Public Health Sciences Froen, Frederik; Nasjonalt folkehelseinstitutt, Division of Epidemiology Geary, Michael; Rotunda Hospital, Parnell Square Hunter, Alyson; Royal Maternity Hospital, Grosvenor Road, BT12 6BB McAuliffe, Fionnuala; University College Dublin, Murdoch, Edile; Royal Infirmary of Edinburgh, NHS Lothian, EH16 4SA., Department of Neonatology Rodriguez, Aryelly; University of Edinburgh, (ECTU) Edinburgh Clinical Trials Unit Ross-Davie, Mary; NHS Education for Scotland, 3rd Floor, Hanover Buildings, 66 Rose Street, EH2 2NN. Scott, Janet; Sands, Victoria Charity Centre, Suite GF2 Ground Floor, 11 Belgrave Road, SW1V 1RB. Whyte, Sonia; Queen's Medical Research Institute, EH16 4TJ, Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health, Norman, Jane; , Queen's Medical Research Institute, EH16 4TJ
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Research methods
Keywords:	Reduced Fetal Movements, Perinatal Mortality, Stillbirth, Neonatal Death, Fetal Growth Restriction

Study Protocol

Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality? - A stepped wedge cluster randomised trial (AFFIRM)

Alexander E P HEAZELL,[1,2] alexander.heazell@manchester.ac.uk

Christopher J WEIR, [3,4] christopher.weir@ed.ac.uk

Sarah J E STOCK,[5 6] sarah.stock@ed.ac.uk

Catherine J CALDERWOOD,[7] catherine.calderwood@scotland.gsi.gov.uk

Sarah CUNNINGHAM-BURLEY,[4] sarah.c.burley@ed.ac.uk

J Frederik FROEN,[8] frederik.froen@fhi.no

Michael GEARY,[9] mppgeary@gmail.com

Alyson HUNTER,[10] alyson.hunter@belfasttrust.hscni.net

Fionnuala M MCAULIFFE,[11] fionnuala.mcauliffe@ucd.ie

Edile MURDOCH,[12] edile.murdoch@nhslothian.scot.nhs.uk

Aryelly RODRIGUEZ,[3,4] aryelly.rodriguez@ed.ac.uk

Mary ROSS-DAVIE,[13] mary.ross-davie@nes.scot.nhs.uk

Janet SCOTT [14] janet.scott@uk-sands.org

Sonia WHYTE [5] sonia.whyte@ed.ac.uk

Jane E NORMAN.[5] jane.norman@ed.ac.uk

1. Maternal and Fetal Health Research Centre, Institute of Human Development, University of Manchester. 2. St. Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, M13 9WL. 3. Edinburgh Clinical Trials Unit, Edinburgh, UK 4. Centre for

Population Health Sciences, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Teviot Place, Edinburgh EH8 9AG. 5. Tommy's Centre for Maternal and Fetal Health, MRC Centre for Reproductive Health, Queen's Medical Research Institute, Edinburgh, EH16 4TJ.6. School of Women's and Infants' Health, University of Western Australia, Crawley WA 6009. (FMM) 7. Chief Medical Officer for Scotland, The Scottish Government St Andrew's House Edinburgh EH1 3DG. 8. Department of International Public Health, Norwegian Institute of Public Health, PB 4404 Nydalen, N-0403 Oslo, Norway, 9. Rotunda Hospital, Parnell Square, Dublin 1, Ireland. 10. Centre for Fetal Medicine, Royal Maternity Hospital, Grosvenor Road, Belfast, BT12 6BB 11. UCD Obstetrics & Gynaecology, School of Medicine, University College Dublin, Ireland. National Maternity Hospital, Dublin, Ireland. 12. Department of Neonatology, Royal Infirmary of Edinburgh, NHS Lothian, Edinburgh, EH16 4SA. 13. NHS Education for Scotland, 3rd Floor, Hanover Buildings, 66 Rose Street, Edinburgh EH2 2NN. 14. Sands, Victoria Charity Centre, Suite GF2 Ground Floor, 11 Belgrave Road, London, SW1V 1RB.

Abstract

Background - In 2013, the stillbirth rate in the UK was 4.2 per 1,000 live births, ranking 24th out of 49 high-income countries, with an annual rate of reduction of only 1.4% per year. The majority of stillbirths occur in normally formed infants, with (retrospective) evidence of placental insufficiency the commonest clinical finding. Maternal perception of reduced fetal movements (RFM) is associated with placental insufficiency and increased risk of subsequent stillbirth.

This study will test the hypothesis that the introduction of a package of care to increase women's awareness of the need for prompt reporting of RFM and standardised management to identify fetal compromise with timely delivery in confirmed cases, will reduce the rate of stillbirth. Following the introduction of a similar intervention in Norway the odds of stillbirth fell by 30%, but the efficacy of this intervention (and possible adverse effects and implications for service delivery) have not been tested in a randomised trial.

Methods - We describe a stepped wedge cluster trial design, in which participating hospitals in the UK and Ireland will be randomized to the timing of introduction of the care package. Outcomes (including the primary outcome of stillbirth) will be derived from detailed routinely collected maternity data, allowing us to robustly test our hypothesis. The degree of implementation of the intervention will be assessed in each site. A nested qualitative study will examine the acceptability of the intervention to women and health care providers and identify process issues including barriers to implementation.

Ethics and Dissemination – Ethical approval was obtained from the Scotland A Research Ethics Committee (Ref 13/SS/0001) and from Research and Development offices in participating maternity units. The study started in February 2014 and delivery of the intervention completed in December 2016. Results of the study will be

submitted for publication in peer-reviewed journals and disseminated to local investigating sites to inform education and care of women presenting with RFM.

Trial Registration

www.clinicaltrials.gov NCT01777022

Version

Protocol Version 4.2, 3rd February 2017

Keywords

Reduced Fetal Movements; Perinatal Mortality; Stillbirth; Neonatal Death; Fetal Growth Restriction.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This trial directly addresses the need for studies of the information given to women regarding fetal movements and the subsequent management of reduced fetal movements identified by Confidential Enquiries into Antepartum Stillbirths, Systematic Reviews and the Stillbirth Priority Setting Partnership.
- A stepped-wedge cluster trial design in combination with routinely collected maternity data allows the trial to be adequately powered to detect a difference in stillbirth as a primary outcome.
- The pragmatic nature of the study represents the potential impact of the introduction of such standardised care into clinical practice.
- The nested qualitative study will provide information regarding the acceptability of the intervention and identify barriers and facilitators to its adoption.
- The lack of information on resource use before and throughout the study period limits the ability to understand the consequences of the intervention on maternity unit workload.

92

INTRODUCTION

Stillbirth

Stillbirth, defined in the UK as a baby with no signs of life after 24 weeks of completed pregnancy [1], remains the major cause of perinatal mortality in high-income environments, with a recent series of papers in the Lancet on stillbirth issue calling for renewed action in this area [2]. There is no single "cause" of stillbirth, and a significant proportion of stillbirths remain unexplained, but fetal growth restriction, maternal hypertension and low socioeconomic status are amongst the identifiable risk factors [3]. The concept that more can be done to reduce stillbirth in the UK and Ireland is supported by data showing a marked variation in rates between resource rich countries, when similar definitions of stillbirth are used [2]. Notably, the UK has a higher rate than comparable resource rich countries such as Germany, Netherlands, New Zealand and Norway with rates in the UK some 50% greater than those of the Netherlands. Disappointingly, the annual rate of reduction in stillbirth from 2000 to 2014 in the UK was only 1.4% compared to 6.8% in the Netherlands and 2.8% in New Zealand [2]. Rates of stillbirth in Scotland (3.7 per 1,000 births in 2014) and Ireland, at (4.4 per 1,000 livebirths in 2013) are similar to rates in England and Wales at 4.2 per 1,000 livebirths (England and Wales, 2014) [4]. The reduction of avoidable harm for women and babies is viewed as a major priority for Government and its agencies throughout the UK and Ireland. Consequently, several initiatives have been developed by national governments in the UK and Ireland including the Scottish Government Stillbirth Working Group, NHS England Saving Babies' Lives Care Bundle and the Welsh Assembly 1000 Lives Plus strategy. These strategies have identified the need for better evidence to guide efforts to prevent stillbirths.

Using a robust priority setting strategy [5] the Lancet Stillbirth's series steering committee identified issues around detection and management of reduced fetal movements (RFM) amongst the top ten key research questions on prevention and

management of stillbirth [6]. This was confirmed in the UK-based Stillbirth Priority Setting partnership involving over 1,700 parents and professionals which identified two relevant issues among the highest ranked research questions regarding stillbirth: i) which investigations identify a fetus at risk of stillbirth after a mother believes she has experienced reduced fetal movements? and ii) would more accessible evidence-based information on signs and symptoms of stillbirth risk, designed to empower women to raise concerns with healthcare professionals, reduce the incidence of stillbirth? [7] Thus, RFM has been identified as a highly-relevant area of study by parents, professionals and researchers.

Reduced Fetal Movements, Stillbirth and Placental Insufficiency

There is a clear association between maternal perception of RFM and late stillbirth dating back over four decades [8]. In a recent series of 2,000 women, the adjusted OR (95% CI) of late stillbirth in women with RFM (compared with controls) was 2.37 (1.29-4.35) [9]. One international study of 1,714 women who experienced a stillbirth found that 30% had noted significant RFM prior to the diagnosis of stillbirth [10]. Although the mechanisms have not been fully delineated, it is likely that RFM and stillbirth are linked by a common pathology, that of placental dysfunction [11]. There is good evidence linking placental dysfunction and RFM. Compared to controls with an active fetus women who have fewer fetal movements on ultrasound scan immediately prior to caesarean section are more likely to have umbilical cord gas measurements indicative of acidaemia, hypoxaemia, and hypercapnia [12]. Women delivering within one week of an episode of RFM show differences in placental structure and function which are reminiscent of those seen in fetal growth restriction (FGR) and stillbirth [13 14]. Additionally, the odds of fetal growth restriction (FGR, defined as being at less than the 10th centile for gestation adjusted birthweight) were greater in women with RFM compared with controls (adjusted OR 1.6, 95% CI 1.1–2.2 [15]). Taken together these

data are strong evidence that placental dysfunction is associated with RFM, and a causative pathway seems likely.

The evidence linking placental dysfunction and stillbirth is even stronger; a systematic review of placental pathology in stillbirths described abnormalities in up to 65% of cases [10]. Amongst the 291 stillbirths in Scotland in 2010, 137 (47%) had evidence of placental dysfunction [16]. Given that the placenta was examined in only 80% of stillbirths, the true prevalence of placental dysfunction is likely to be higher. In addition, between 20%-40% of stillborn babies are reported to have FGR, as defined by a birthweight less than the 10th centile [17]. Additionally, the Lancet report notes that "placental pathologies accounted for one in four deaths across all gestational ages, and were contributory or causal in more than half of cases" [6]. Given that stillbirth is strongly related to placental dysfunction, and RFM is a "biomarker" of placental dysfunction then better management of women presenting with RFM focussing on the detection of placental dysfunction might reduce the risk of stillbirth.

Formal Fetal Movement Counting

Although prenatal detection of FGR is improved by fetal movement counting [18], a systematic review [19], and a large and influential cluster randomised trial (which dominates the systematic review) showed that routine fetal movement counting using the count to ten charts had no effect on perinatal mortality [20]. Thus, the National Institute for Health and Social Care Excellence (NICE) recommended that "Routine formal fetal movement counting should not be offered" [21]. Importantly, the large cluster randomised trial tested a specific alarm limit for RFM, but did not recommend a specific management strategy for women who did present with RFM. There were two important observations from this study, firstly that in both groups the perinatal mortality rate was lower than contemporary or subsequent periods in the UK and secondly that more women in the fetal movement counting arm came in with a live baby who subsequently died compared with the control arm (19 vs 11), suggesting

that one reason the strategy failed to reduce perinatal mortality was inadequate investigation and management of those presenting with RFM [20].

Optimal strategy for determining RFM to prompt maternal presentation to the maternity service

Maternal concern about RFM is a common reason to contact maternity services with between 6-15% of women presenting during the third trimester.[22 23] Nevertheless, delays in reporting RFM to maternity care providers may increase the risk of adverse outcome.[24 25] The lack of good-quality information given to women about fetal movements has been highlighted as an example of suboptimal care in Confidential Enquiries into Antepartum Stillbirth.[26 27] Qualitative studies suggest that women frequently perceive RFM two days prior to the diagnosis of fetal death, and in some cases contractions were misinterpreted as fetal movements.[28] Therefore, giving information to women regarding fetal movements and when they should be concerned about RFM is a key component of an intervention to reduce stillbirth.

However, giving clear information about RFM can be challenging as there is no uniform threshold of fetal movements below which perinatal morbidity increases [23], and no evidence that a specific threshold performs better than maternal perception of reduced fetal movements alone [8]. Current guidelines from the RCOG and PSANZ [29 30], informed by a large Norwegian study [31] suggest that it is maternal *perception* of decreased fetal movement which is important. Therefore, information for pregnant women in this study (shown in Supplementary File 1) described the importance of fetal movements, the need to get to know normal fetal activity, how fetal movements change in late pregnancy and who to contact if the mother perceives RFM. The educational package aimed to ensure that these messages were reinforced by staff behaviour at antenatal contacts.

Optimal strategy for investigation and management of women presenting with RFM.

A recent systematic review found there are no proven strategies for the investigation and management of women presenting with RFM [32]. Cardiotocography (CTG) is routinely used to ascertain fetal wellbeing, and it is the cornerstone of the RCOG guideline [30]. However, data from Norway, suggests that ultrasound assessment of fetal size is often the most helpful investigation, performing well on both an absolute basis, and compared with other interventions [33]. In a series of over 3,000 women with RFM, ultrasound (including measurement of fetal biometry and liquor volume) was found to be useful in detecting abnormalities in 11.6% of scans. In 71% of women in whom an abnormality was found, ultrasound was the only technique that detected an abnormality. Additionally, 85% of abnormalities detected by ultrasound, were important in informing the clinical management of the woman [33]. These data are supported by a smaller UK study which found that abnormalities detected on CTG or ultrasound scan were most strongly associated with adverse outcome in women with RFM, with identification of abnormal estimated fetal growth centile on scan being the test most highly predictive of poor outcome [34]. Perhaps this is not surprising, given the strong association between RFM and placental dysfunction and the central importance of ultrasound in the identification and management of small for gestational age babies [35]. Given these data, it is concerning that a survey of clinicians in Scotland showed that fewer than 5% would routinely refer women with RFM for ultrasound examination (unpublished data from June 2012), and a survey of 223 UK midwives and obstetricians described that 17.9% of respondents would perform an ultrasound scan [36]. These views of clinicians may reflect the variable quality of local guidelines, which are frequently not based on national recommendations, even those for which there is strong evidence [37].The variation in information given to women and subsequent management of RFM has been highlighted as sources of suboptimal care in two confidential enquiries into antepartum stillbirth [26 27]. Therefore, we believe that current investigation of women presenting with RFM is inadequate, hence using the best available evidence, we have drafted what we consider to be a robust evaluation

protocol for investigation of women with RFM.

Potentially efficacy of a package of intervention for RFM

Supportive data for the package of interventions used in this study (information for women and standardised management protocol) comes from a large observational "clinical quality improvement study" in Norway which found a significant fall in rates of stillbirth (from 3.0/1,000 to 2.0/1,000 [OR 0.67 95% CI 0.48–0.93]) after the introduction of an intervention package consisting of written information for women about awareness of RFM combined with consensus guidelines for health professionals about their management [31]. Although this study was not randomised, and therefore constitutes only level II-3 evidence, it has informed recommendations from the Royal College of Obstetricians and Gynaecologists (RCOG) and Perinatal Society of Australia and New Zealand (PSANZ) that "women should be advised to be aware of their baby's individual pattern of movements and that if they are concerned about a reduction in or cessation of fetal movements …..they should contact their maternity unit" [29 30].Following initial publication of the Norwegian study, a re-analysis was required as discrepancies between stillbirth rates in the study and the Medical Birth Registry of Norway were identified. This reanalysis found the reduction in stillbirth rates was of borderline statistical significance (OR 0.72, 95% CI 0.50-1.03). The authors concluded that further studies were needed to determine whether this approach was associated with a reduction in stillbirth [38].

Importantly, in the Norwegian study, there was no increase in the proportion of women who presented with RFM when rates were compared before and after the intervention [31]. However, women with RFM presented significantly earlier to hospital than they had hitherto, potentially allowing time for intervention to reduce perinatal mortality. These data suggest that a package of interventions encouraging women with RFM to present early to hospital, combined with a structured approach to their management might reduce rates of stillbirth without contributing to a large increase in

admissions antenatally.

Potential harms of a package of care around increased awareness and optimised management of RFM

Any clinical intervention which aims to improve outcomes also has the ability to do harm. Thus, it is essential that the intervention proposed is rigorously evaluated using the gold standard technique of a randomised trial, rather than being introduced as a service development. When the study began, there was a small window of opportunity to do this, as the enthusiasm to improve current management of RFM is such that routine introduction of the package of care is unlikely to be delayed much further than the current scheduled end date of this study. Possible harms of a package of care consisting of a management plan for identification and delivery of the "at risk" fetus, together with strategies for increasing pregnant women's awareness of the need to report early include increased maternal anxiety and increased intervention (including hospital admission, induction of labour and Caesarean section) which itself is associated with pregnancy related complications. The available evidence is reassuring on some of these issues. A systematic review of 23 publications from 16 studies found three studies involving 2,030 women addressing maternal concern and an additional three studies involving 1,468 women investigating maternal-fetal attachment. These demonstrated no evidence of increased maternal anxiety and results regarding maternal-fetal attachment were discordant.[39] In the Norwegian service development study, the package of care increased rates of follow up of women, but there was no increase in admissions overall, admissions for induction or admissions for emergency caesarean section [31] – again, whilst reassuring these outcomes require formal evaluation in a randomised and relevant setting to the UK and Republic of Ireland. The final possible harm of the package is around increased resource use, and the opportunity cost of focussing on RFM rather

than other potential methods to prevent stillbirth.

RATIONALE

The aim of this study is to test the hypothesis that a package of interventions consisting of strategies for increasing pregnant women's awareness of the need to report early when they perceive a reduction in fetal movements, followed with a management plan for identification and delivery of the "at risk" fetus in such women, will reduce rates of stillbirth.

STUDY OBJECTIVES

Primary Objective

The primary objective is to answer the research question 'Does the introduction of a protocol for detection and management of decreased fetal movements reduce rates of stillbirth?' The secondary objectives are to answer the following research questions:

- What is the effect of the intervention on rates of caesarean section and induction of labour?
- What is the effect of the intervention on rates of admission to the neonatal intensive care unit?
- What is the effect of the intervention on the proportion of women with FGR remaining undelivered by 40 weeks gestation?
- What is the acceptability of such a package of care to pregnant women and their health care providers?
- What other process outcomes are influenced by the intervention, such as health care provider/patient interactions?

ENDPOINTS

Primary Outcome

The primary endpoint is stillbirth (antepartum and intrapartum). We will use the UK definition of stillbirth which is "a baby delivered without signs of life after 23^{+6} weeks" [4]. Where gestation is uncertain we will include all babies with a birth weight of 500g or more.

Secondary Endpoints

Other measures of perinatal mortality including:

- Stillbirth at 37 weeks gestation and above
- Stillbirth at 28 weeks gestation and above (WHO definition of stillbirth)
- Stillbirth at 22 weeks gestation and above (international stillbirth alliance definition)
- Stillbirths amongst normally formed infants of 22 weeks gestation and above, 24 weeks gestation and above, 28 weeks gestation and above and 37 weeks gestation and above.
- Perinatal mortality (defined as stillbirth at 24 weeks gestation and above and deaths in the first seven days of life)
- Rates of caesarean section
- Rates of induction of labour (for any indication)
- Rates of elective delivery (induction of labour and caesarean section prior to the onset of labour) overall
- Rates of induction of labour at 39 weeks gestation or later
- Mean gestation at induction of labour

- Rates of admission to the neonatal unit (and their reasons)
- Rates of admission to the neonatal unit for more than 48 hours
- Rates of admission to the neonatal unit for term babies (those born at 37 weeks 0 days or greater)
- Proportion of infants with fetal growth restriction (less than the 5th centile, customised for gender) remaining undelivered at or after 40 weeks gestation
- Birthweight centile (according to the Intergrowth birthweight centile calculator at https://intergrowth21.tghn.org)
- Rates of spontaneous vaginal delivery

Other secondary outcomes are the baby parameters:

- Gestation at birth
- Proportion of babies born preterm (<37 weeks gestation)
- Gender of the baby
- Birthweight of the baby
- Apgar score at 5 minutes
- Proportion of babies with 5 minute Apgar score < 7
- Proportion of babies with 5 minute Apgar score < 4
- Resuscitation required at birth

We will also collect the following data: maternal age, maternity unit of delivery, birthweight, gestation of delivery, parity, gestation, sex, smoking (current and ever), maternal body mass index (BMI), number of babies (one or more), ethnicity (to allow a customised birthweight centile to be generated), method of delivery, deprivation category (where available) and other neonatal variables including Apgar score and encephalopathy. Adjustment will be made for the following variables: (maternal age,

maternity unit of delivery, parity, smoking status, maternal BMI, number of babies [one or more] and ethnicity)

STUDY DESIGN

This is a multicentre, stepped wedge cluster randomised trial of a package of care consisting of a management plan for identification and delivery of the 'at risk' fetus, together with strategies for increasing pregnant women's awareness of the need to report RFM early. The trial developed from a planned quality improvement project proposed by the Scottish Government to reduce stillbirths. This was planned to emphasise the importance of fetal movement monitoring and was to be rolled out to all NHS maternity units in Scotland. However, prior to this change it was agreed that the roll out could be performed in such a way as to allow the assessment of the effect of the intervention, the stepped-wedge design would be the natural choice in this circumstance.

The study will take place in participating hospitals in the UK and Ireland (a complete list is available http://www.crh.ed.ac.uk/affirm/randomised-hospitals/). A nested qualitative study will examine the acceptability of the intervention to patients and health care providers and identify process issues (barriers to implementation). Clinical audit (detailed in Appendix 3) conducted after the change in practice will be used to determine the effect of interventions on process outcomes (e.g. number of women presenting with reduced fetal movements, interval between perceiving reduced fetal movements and presentation to hospital, number of ultrasound scans, number of admissions for induction of labour). A diagram indicating randomisation of hospital groupings in the stepped wedge design is shown in Figure 1.

The interventions will be introduced over a 32 month period. Data will be collected over a 36 month period. Data in the 'active phase' after introduction of the

intervention will be compared to data in the 'control phase' – the period during which usual care processes in study sites are followed from study start to the time of introduction of the intervention. Given that it will take individual units some time (a) to effect change in management in their unit from time of introduction of the intervention and (b) that it will take some time for this change in practice to impact on clinical outcomes, we plan a "washout" period of two months after the introduction of the intervention during which data will not be included in either group for analysis (Figure 1). Data will be collected four months after the last birth, a further two months has been included for data analysis, giving a total study duration of 42 months.

STUDY POPULATION

Number of participants

Participants will be those delivering at all the sites over the study period (36 months). All eligible women will be recruited to the cluster randomised controlled trial. Based on previous delivery numbers, after accounting for a washout period of two months (and assuming no withdrawals or losses to follow up) this is estimated to be a total of around 143,140 women per annum. A subset of around 30 participating women and 30 midwives, sonographers and obstetricians will be recruited to the nested qualitative study, which is based in the Scottish sites.

Inclusion criteria

We will include all women delivering at one of the participating maternity units for the duration of the study. Women who have been seen at any of the maternity units but who deliver at home will not be included. The duration of the study will be 42 months from the start of the trial (01/02/2014). For practical reasons, participants for the nested qualitative study will be recruited from the participating units in Scotland.

Exclusion criteria

We will exclude women as follows:

- Women for whom data on delivery outcomes is still unavailable four months after the date of delivery
- Women delivering in the "washout" period in each unit.

Members of the trial management group and participants who do not speak/understand English will be excluded from participating in the nested qualitative study.

Identifying participants

Women will be identified from those whose data is included in routine data returns from each unit. Potential participants for the nested qualitative study will be identified from those attending antenatal clinics in participating hospitals, and/or local staff.

Consenting participants

The main study is a stepped wedge cluster randomised trial of a package of care which would be introduced in many of the participating units regardless of whether the trial was on-going or not and the trial uses only routinely collected data on participants. The ethics committee indicated that formal individual patient consent is not necessary for the main trial. Participants in the nested qualitative study will be asked for individual consent.

Screening for eligibility

As participants are not directly recruited we will not perform any specific screening tests for this aspect of this project. Participants for the nested qualitative study will be: (i) Pregnant women attending hospitals who are participating in the main trial in Scotland. Purposive sampling will ensure that the final sample set includes women who have and who have not experienced RFM, both before and after the introduction of the intervention; (ii) Hospital staff (including midwives, ultrasonographers and

obstetricians/radiologists) working in participating hospitals in Scotland. There will be no specific screening tests for eligibility for the nested qualitative study, except that women who have experienced a stillbirth in the index pregnancy will not be approached.

Ineligible and non-recruited participants

Potential participants for the nested qualitative study who are not approached or who decline will have no specific interventions / procedures.

Withdrawal of Study Participants

The nature of a cluster randomised study is such that it is not possible for the participant to withdraw from the "cluster" unless she changes maternity unit part way through her pregnancy. We plan to collect routinely recorded anonymised data; patients have the right to opt out of having their data used – if this happens their data would be excluded from the study database (e.g. under the Confidentiality and Security advisory Group Report 2002 and the Data Protection Act (1998) requirements for fair processing of data). Participants in the nested qualitative study who wish to withdraw will be allowed to do so. Their data will be retained and used, unless they additionally indicate that they wish to withdraw their data.

RANDOMISATION

Randomisation Procedures

This is a cluster-randomised, stepped-wedge design trial wherein maternity units rather than individual patients are randomised. All units will implement the fetal movement monitoring intervention at some point during the trial; the random element is the time point at which this will occur, the so-called "step" of the stepped-wedge design. Participating maternity units will be blinded to their randomly allocated time point until the time this is required to be revealed to enable the necessary training in the implementation of the intervention to be delivered. Primary and secondary

outcomes of the trial will be gathered in a blinded manner via routinely collected data sources.

Maternity units which are in close proximity to each other will be grouped for the purposes of randomisation. This will assist with the feasibility of delivering the training for and implementation of the intervention. Furthermore, this local synchronisation of the intervention implementation will minimise the chances of contamination (introduction of the intervention prematurely) from maternity units which have already implemented the intervention to those not yet randomised.

The order in which the groups of maternity units step in to implement the intervention will be determined by computer generated random numbers from a uniform distribution. The randomisation list will be held by the Edinburgh Clinical Trials Unit (ECTU). The identities of the research team staff whose roles in the trial require them to be unblinded to randomisation codes will be recorded in the trial master file (TMF).

Treatment Allocation

Participating sites will be randomised to different schedules for implementing the intervention. All units will be providing conventional treatment at baseline according to local practice – this is the treatment established before the study starts. Sites will be randomised to “active” treatment in turn as described above. Active treatment will consist of a package of care consisting of a management plan for identification and delivery of the ‘at risk’ fetus, together with strategies for increasing pregnant women’s awareness of the need to report RFM early. The recommended management plan for identification and delivery of the “at risk” fetus is shown in Figure 2. Practice change in the active units will be achieved by: (i) written/email information to all clinicians (doctors, midwives and ultrasonographers) in each unit about the study protocol and amendment of the local protocol for Reduced Fetal Movements (RFM) to that of the study protocol; (ii) a short web-based training package taking approximately one hour to complete for all clinicians in each centre and (iii) training /information sessions to

run in each unit and (iv) posters in each unit to describe the practice change. Strategies for encouraging clinicians to increase pregnant women's awareness of fetal movement will include all the above and also a fetal movement leaflet for pregnant women (shown in Supplementary Information 1). The Norwegian quality improvement study showed inconclusive results regarding the effect of the intervention in non-European women.[40] To attempt to address this, the AFFIRM information leaflet was available in 12 languages including: Arabic, Bengali, English, Hindi, Hungarian, Latvian, Lithuanian, Mandarin, Polish, Russian and Urdu. Furthermore, by including staff education which highlighted the need to ask women about fetal movements in routine antenatal consultations as many women as possible should have received information about what to do if they perceive RFM.

Once units have begun active treatment it is not anticipated that they will return to conventional treatment. We will conduct an audit of women presenting with reduced fetal movements and assess the proportion of staff completing the online training to assess the extent to which sites have followed the intervention plan. Units will be informed about treatment allocation as near as possible to the implementation of the "active" treatment. For practical purposes, we anticipate that each unit will need around three months' notice before the "active" treatment is introduced, hence units will be informed of the timing of their treatment allocation (step) three months before the active treatment is due to start. The treatment allocation will not be administered blind and there are no restrictions on concomitant care or other interventions during the study, hence there is no need for emergency unblinding and there are no stopping rules for the study.

DATA COLLECTION

For the main trial, data will be accessed from the information routinely collected during the clinical management of the patient. For consistency, we will normally only

include data items which become available within four months after the delivery date in question, although we may seek advice from the independently-chaired trial steering committee (TSC) about exceptions as they arise. Different data sources will be used for different regions of the study: (i) In Scotland the source data will be SMR2 and the Scottish Birth record, (ii) In Ireland the source data will be the National Perinatal Reporting System (NRPS http://www.esri.ie/health_information/nprs), (iii) In Northern Ireland, the source data will be the Northern Ireland maternity Statistics database (NIMATS), (iv) In England and Wales, the source data will be the ONS, or other relevant body. Data will be collected retrospectively on an annual basis from all sources. We will assume that data unavailable four months after the woman delivered is likely to be unobtainable (but see note in Study Design section above). Thus, data on the first year of the study will be collected at month 16; data on the second year will be collected at month 28 etc.

Data are routinely collected. A formal request for data access will be made at the start of the study. This will require (i) in Scotland – Privacy Advisory Committee approval and a formal approach to NHS Scotland Information Services Division (ISD) (ii) in Ireland a formal approach to NRPS (iii) NIMATS in Northern Ireland (iv) in England and Wales a formal approach will be made to the relevant bodies.

Data will then be sent to the electronic Data Research and Innovation Service (eDRIS) National Safe Haven (NHS National Services Scotland) by secure file transfer protocol (or other similar) for storage and subsequent analysis within a secure project area (dedicated to the AFFIRM study). Further information on the National Safe Haven is available at http://www.isdscotland.org/Products-and-Services/eDRIS/Becoming-an-eDRIS-User/#NSS-National-Safe-Haven. Briefly, the National Safe Haven is located on a secure server, in which trusted and authorised researchers can analyse individual level data while maintaining the utmost

confidentiality. It is anticipated that all study analysis will be done within the Safe Haven, using one of the available statistical packages (e.g. R, SPSS).

Identifiers on Scottish data within the National Safe Haven are concealed from researchers. Data from outwith Scotland will be anonymised before submission to the National Safe Haven. We propose that data submitted to the National Safe Haven will be "anonymised" by the data provider. However, we propose that the anonymisation link will be retained at the source so that it will be possible to re-link data retrospectively. The rationale for retaining the ability of local data guardians to re-link data is because it is important to retain the possibility of identifying individual patients retrospectively. Examples include: (i) It is possible that some additional important data may be available at a late stage on individual participants – e.g. in the scenario where the woman or baby had a major adverse event and spent a long time in hospital before discharge or death and (ii) Although our protocol and outcome analysis does not require identifiable data, we believe this will be a 'once in a lifetime" study, and that subsequent secondary analyses could yield important information for patients and for policy makers. If retrospective identification is not possible, this will limit further analysis. One likely example of future analyses is to determine the effect of the intervention on different causes of stillbirth. This is outwith the scope of the current protocol, but could be done relatively straightforwardly, by linking nationally recorded information on "cause" of stillbirth to our study database. We anticipate that such additional analyses would require additional ethics approval, but without a process by which to re-link data, it will not be possible to perform such subsequent analyses.

All Investigators and study site staff involved with this study will comply with the requirements of the Data Protection Act 1998 (or equivalent for those outwith the UK) with regard to the collection, storage, processing and disclosure of personal

information and will uphold the Act's core principles. Published results will not contain any personal data that could allow identification of an individual participant.

In addition to the data recorded above, all sites will be asked to provide a copy of their guidelines around (i) maternal awareness of RFM and (ii) management of women presenting with RFM. Copies of guidelines will be sought by the study office (a) at the start of the study (b) immediately before initiation of the intervention in each specific unit and (c) six months after initiation of the intervention in each specific unit.

For the nested qualitative study, we will perform interviews of healthcare workers and a small nested cohort of pregnant women about their experiences of fetal movement and of this intervention. We shall ensure a diversity of age and include nulliparous and multiparous women (n=30 in total). Ten interviews will be conducted with each of the following groups of health care providers: obstetricians, midwives and sonographers/radiologists. The interviews will take a semi-structured format (sensitising and piloting interviews will be conducted prior to the commencement of the trial and in the first month of the nested qualitative study). This format will ensure the same categories of data will be obtained from each participant but also allow individual responses to be fully explored.

STATISTICS AND DATA ANALYSIS

Sample size calculation

The sample size is the number of women delivering in hospitals participating in the study. This was initially planned to include sites in Scotland, totalling around 58,000 deliveries per year with 16 consultant led maternity units, 20 smaller units each delivering less than 350 babies per year, and seven units delivering less than five births per year. The units involved in Perinatal Ireland (an all-Ireland research consortium across 7 academic sites in Ireland currently funded by the Health

Research Board, Ireland) have 50,000 births per year with seven large sites. Combining one or two of the smaller units and one larger unit into a single "hospital group" for each local area could provide 24 hospital "groups" – the details of hospital groupings will be reviewed and finalised immediately prior to randomisation. In total, 36 sites expressed interest in participating in the study, although 2 were unable to participate in the study and withdrew before randomisation. In total, 34 units were randomised, these were situated throughout the UK and Ireland (10 in England, 4 in Ireland, 15 in Scotland and 5 in Wales) with 143,140 births per annum.

We calculated statistical power using the methodology for stepped wedge designs proposed in Hussey and Hughes (2007).[41] First, we analysed stillbirth event data from the Scottish Perinatal and Infant Mortality and Morbidity Report (SPIMMR) covering years 2005-2010 [16] to determine estimates of between- and within-unit variability in stillbirth rate. Analysis was by generalized linear mixed model for binary outcomes. The power calculation, as per equations (#7) and (#8) in [41] assumed: significance level 5%; analysis by generalized linear mixed model; deliveries equally distributed across hospital groupings; baseline stillbirth rate 0.438% [16]; cluster coefficient of variation 0.333.

Finally, the statistical power depends on the number of groups in which the intervention is implemented at each stage of the stepped wedge design and the duration of recruitment at each "step". Our study design proposes sequential introduction of the intervention into three hospital groups at a time in eight steps at four month intervals. This would give 92.4% power to detect a 30% risk reduction under the intervention and 80.7% power to detect a 25% reduction. A 30% risk reduction was seen in the Norwegian study; the anticipated effect sizes of 25% and 30% relative reduction take into account that the intervention will not have the power to reduce all stillbirths, since 20% of stillbirths in Ireland [42] and 15% in Scotland [16] are associated with congenital anomaly.

The power actually achieved in the study will be slightly lower, as deliveries during the two month "transition" period following implementation of the intervention in a site will not be included in the analysis. The effect of this was explored using the Stata function steppedwedge,[43] which showed the statistical power would become 88.2% (30% risk reduction) and 74.6% (25% risk reduction). It is anticipated that unavailability of data and women asking to withdraw their data will be less than 1%.

Proposed analyses

For the binary primary and secondary outcomes, data will be analysed by generalized linear mixed model with a random effect for hospital and fixed effects for the intervention implementation and study time period. A site by intervention interaction random effect will be included in the model and retained if it explains an important proportion of the variability in outcomes. The primary analysis of data will be on an intention to treat basis (the design of the trial means it is not possible to determine individual patient /caregiver compliance with the intervention). An "on treatment" variable will be calculated for which women will be grouped as active or control according to when the intervention was actually implemented in their site, instead of when the site was randomised to implement the intervention. The primary outcome will be reanalysed in two sensitivity analyses. Firstly, we will perform the analysis according to the actual timing of the implementation of the intervention rather than the randomised timing of the intervention using the "on treatment" classification. Secondly, we will perform the analysis in the subgroup of sites who were deemed to have implemented the intervention effectively according to the perception of the Principal Investigator at each site. The accuracy of this perception will be confirmed with the findings of a site audit (details in Appendix 3). There will be no attempt to correlate the impact of the intervention according to the results of the site audit.

There are no planned imputations for missing data. However, if the missing data rate for smoking status during pregnancy is relatively high an imputation technique will be devised. The imputation method will be informed using smoking history at booking and age at delivery [44]. A pre-specified subgroup analysis will be performed for babies with and without congenital anomalies, and will be implemented by testing for an intervention by congenital anomaly interaction added to the generalised linear mixed model described above. No formal interim analyses for efficacy or safety will be performed. A full statistical analysis plan will be finalised prior to locking of the study database.

Qualitative Data

For the nested qualitative study, the data will be audio recorded and transcribed. The data will be coded thematically and an analytical framework developed to make sense of patient experience of fetal movement and the intervention and also health care providers' perspectives and experiences. NVivo will be utilised to support the analysis.

Process outcomes

The process outcomes being assessed by the (rates of induction of labour, number of women presenting with reduced fetal movements, interval between perceiving fetal movements and presenting to hospital) will be analysed using the same methods as for the main trial, with the exception of the continuous outcome (interval between perceiving fetal movements and presenting to hospital) which will be analysed using a normal linear mixed model.

ADVERSE EVENTS

This is not a Clinical Trial of an Investigational Medicinal Product (CTIMP) so adverse events will not be formally reported. Stillbirth and other measures of fetal and

maternal morbidity are outcomes of the study. The purpose of the intervention is to reduce such adverse events. Therefore, due to the low risks for this trial, a separate DMC is not required and the Trial Steering Committee (TSC) will cover any responsibilities normally allocated to a DMC. If considered necessary, the TSC may review unblinded data for the study, including morbidity and mortality indices. No other adverse event reporting will be undertaken.

TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

The trial will be coordinated by a Project Management Group, consisting of the grant holders and the Trial Manager. The Chief Investigator (JN) will lead the project management group. The Trial Manager will oversee the study and will be accountable to the Chief Investigator. A TSC will be established to oversee the conduct and progress of the trial. The terms of reference and a draft template for reporting will be ratified in one of the early meetings of the TSC.

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the co-sponsors (ACCORD: Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian, Sponsor contact: ray.french@ed.ac.uk), research ethics committee (REC) review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

Study monitoring and audit

The sponsor determined that as no individual participants were recruited to the intervention, and it was not a clinical trial of an investigational medicinal product (CTIMP) no formal monitoring and audit was required.

Good Clinical Practice and Ethical Conduct

The study will be conducted in accordance with the principles of the research governance framework operational and good clinical practice in the relevant country. A favorable ethical opinion has been obtained from the Scotland A REC (Reference 13/SS/0001) and local research and development approval has been obtained prior to commencement of the study.

Local study investigator(s) will be appointed to each site (or for small units, groups of sites). S/he will be responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments.

STUDY CONDUCT RESPONSIBILITIES

Protocol amendments

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, will be reviewed and approved by the Chief Investigator and Sponsor. Amendments to the protocol will be submitted in writing to the appropriate REC and local Research and Development (R&D) department for approval prior to participants being enrolled into an amended protocol.

Protocol violations and deviations

Investigators will not implement any deviation from the protocol without agreement from the Chief Investigator and appropriate REC and R&D department approval except where necessary to eliminate an immediate hazard to trial participants. In the event that an Investigator needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded. If this necessitates a subsequent protocol amendment, this will be submitted to the REC, and local R&D department for review and approval if appropriate.

Serious breach requirements

A serious breach is one which is likely to effect to a significant degree (a) the safety or physical or mental integrity of the participants of the trial; or b) the scientific value of the trial. If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) will be notified within 24 hours. It will be the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and, if so, report it to the REC.

All violations will be assessed by the sponsor(s) to ascertain if they meet the criteria for a serious breach. If the sponsor(s) deem the incident to be a violation that does not constitute a serious breach from the protocol when identified, corrective and preventative actions will be taken where appropriate and they will be recorded in file notes, held within the TMF and ISF.

Study record retention

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

End of study

The end of study date was finalised in the protocol after the study commenced; the agreed end of study date is 31/12/2016. The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with good clinical practice guidelines. The clinical study report will be used as the basis for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

DISCUSSION

The data provided by this study will inform the information given to women about reduced fetal movements and their management when they present to maternity

services; which has been recurrently identified by Confidential Enquiries into antepartum stillbirths as suboptimal [26 27]. Data from the AFFIRM study will be able to be compared to results from two other active studies which aim to improve mothers awareness and reporting of reduced fetal movements. My Babies Movement (ACTRN 12614000291684) is stepped-wedge cluster trial of a mobile phone application to help women get to know their baby's movements, to be mindful of movements every day and not to wait to report concerns to their maternity care provider. The Mindfetalness study (NCT02865759) is a cluster trial of 39,000 women randomised to routine antenatal care or the Mindfetalness brochure and website.[45] Women participating in the Mindfetalness process will spend 15 minutes each day getting to know their babies movements and will specifically be encouraged to contact their health provider if their perceive reduced fetal movements. This primary outcome of this study is an Apgar score <7 at 5 minutes; stillbirth and perinatal deaths will be recorded as tertiary endpoints of this study.[45] These large studies will provide much needed robust evidence to determine whether increased maternal awareness of reduced fetal movements combined with a standardised management protocol to identify acute or chronic fetal compromise can reduce stillbirth [32].

PEER REVIEW

This project has been peer reviewed internally, and was externally peer reviewed during the process of securing funding from the Chief Scientist's Office of the Scottish Government, Tommy's and Sands.

FUNDING

The AFFIRM study is investigator initiated and funded by Chief Scientist Office, Scottish Government (CZH/4/882), Tommy's and Sands, the Stillbirth and Neonatal Death Charity. CJW was supported in this work by NHS Lothian via the Edinburgh

Clinical Trials Unit. AEPH is supported by a Clinician Scientist fellowship from the National Institute for Health Research (NIHR; CS-2013-009). This protocol presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the support of Perinatal Ireland and Dr Mary Higgins (University College Dublin, National Maternity Hospital, Dublin).

CONTRIBUTIONS

Contributors AEPH, CJW, SJES, CJC, SCB, MRD, SW and JEN were involved in developing the trial design. AEPH, CJW, SJES, AR and JEN were involved in drafting and revision of the article. CJW and AR were involved in drafting the statistical aspects of the protocol. JS provided feedback on behalf of a stakeholder organisation. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS, SW and JEN were involved in preparing the overall study design. AEPH, JEN and MRD prepared education videos for online training. AEPH, SJES, SJS, MG, AH, FMM and JEN facilitated recruitment of sites. AEPH, CJW, SJES, CJC, SCB, JFF, MG, AH, FMM, EM, AR, MRD, JS, SW and JEN will be involved in the collection, management, analysis and interpretation of data and final writing of the trial report.

COMPETING INTERESTS

None declared.

ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
BMI	Body Mass Index
CTG	Cardiotocograph
CTIMP	Clinical Trial of an Investigational Medicinal Product
ECTU	Edinburgh Clinical Trials Unit
FGR	Fetal growth restriction
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Social Care Excellence
NIHR	National Institute for Health Research
NIMATS	Northern Ireland Maternity Statistics database
NRPS	National Perinatal Reporting System
ONS	Office of National Statistics
PSANZ	Perinatal Society of Australia and New Zealand
RCOG	Royal College of Obstetricians and Gynaecologists
R&D	Research and Development
REC	Research Ethics Committee
RFM	Reduced Fetal Movements
SPIMMR	Scottish Perinatal and Infant Mortality and Morbidity Report
TMF	Trial Master File
TSC	Trial Steering Committee
WHO	World Health Organisation

REFERENCES

1. Curtis L, Burns A. Unit Costs of Health and Social Care 2015 Canterbury: Personal Social Services Research Unit, The University of Kent, 2015.
2. Warland J, O'Brien LM, Heazell AE, Mitchell EA. An international internet survey of the experiences of 1,714 mothers with a late stillbirth: the STARS cohort study. *BMC pregnancy and childbirth* 2015;15:172.
3. Flenady V, Koopmans L, Middleton P, Froen JF, Smith GC, Gibbons K, et al. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet* 2011;377(9774):1331-40.
4. Manktelow BM, Smith LK, Seaton SE, Hyman-Taylor P, Kurinczuk JJ, Field DJ, et al. Perinatal Mortality Surveillance Report - UK Perinatal Deaths for births from January to December 2014. Leicester:: The Infant Mortality and Morbidity Group, Department of Health Sciences, University of Leicester., 2016.
5. Sadovsky E, Polishuk WZ. Fetal movements in utero: nature, assessment, prognostic value, timing of delivery. *Obstet Gynecol* 1977;50(1):49-55.
6. Flenady V, Middleton P, Smith GC, Duke W, Erwich JJ, Khong TY, et al. Stillbirths: the way forward in high-income countries. *Lancet* 2011;377(9778):1703-17.
7. Heazell AE, Whitworth MK, Whitcombe J, Glover SW, Bevan C, Brewin J, et al. Research priorities for stillbirth: process overview and results from UK Stillbirth Priority Setting Partnership. *Ultrasound Obstet Gynecol* 2015;46(6):641-7.
8. Heazell AE, Froen JF. Methods of fetal movement counting and the detection of fetal compromise. *J Obstet Gynaecol* 2008;28(2):147-54.
9. Stacey T, Thompson JM, Mitchell EA, Ekeroma AJ, Zuccollo JM, McCowan LM. The Auckland Stillbirth study, a case-control study exploring modifiable risk factors for third trimester stillbirth: methods and rationale. *The Australian & New Zealand journal of obstetrics & gynaecology* 2011;51(1):3-8.

10. Ptacek I, Sebire NJ, Man JA, Brownbill P, Heazell AE. Systematic review of placental pathology reported in association with stillbirth. *Placenta* 2014;35(8):552-62.

11. Warrander LK, Heazell AE. Identifying placental dysfunction in women with reduced fetal movements can be used to predict patients at increased risk of pregnancy complications. *Medical hypotheses* 2011;76(1):17-20.

12. Vintzileos AM, Fleming AD, Scorza WE, Wolf EJ, Balducci J, Campbell WA, et al. Relationship between fetal biophysical activities and umbilical cord blood gas values. *Am J Obstet Gynecol* 1991;165(3):707-13.

13. Warrander LK, Batra G, Bernatavicius G, Greenwood SL, Dutton P, Jones RL, et al. Maternal perception of reduced fetal movements is associated with altered placental structure and function. *PloS one* 2012;7(4):e34851.

14. Winje BA, Roald B, Kristensen NP, Froen JF. Placental pathology in pregnancies with maternally perceived decreased fetal movement--a population-based nested case-cohort study. *PloS one* 2012;7(6):e39259.

15. Holm Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Froen JF. Maternal characteristics and pregnancy outcomes in women presenting with decreased fetal movements in late pregnancy. *Acta Obstet Gynecol Scand* 2009;88(12):1345-51.

16. Healthcare Improvement Scotland. Scottish Perinatal and Infant Mortality and Morbidity Report 2010. Edinburgh: Healthcare Improvement Scotland, 2012.

17. Gardosi J, Kady SM, McGeown P, Francis A, Tonks A. Classification of stillbirth by relevant condition at death (ReCoDe): population based cohort study. *BMJ (Clinical research ed* 2005;331(7525):1113-7.

18. Saastad E, Winje BA, Stray Pedersen B, Froen JF. Fetal movement counting improved identification of fetal growth restriction and perinatal outcomes--a multi-centre, randomized, controlled trial. *PloS one* 2011;6(12):e28482.

19. Mangesi L, Hofmeyr GJ, Smith V, Smyth RM. Fetal movement counting for assessment of fetal wellbeing. *Cochrane Database Syst Rev* 2015(10):CD004909.

20. Grant A, Elbourne D, Valentin L, Alexander S. Routine formal fetal movement counting and risk of antepartum late death in normally formed singletons. *Lancet* 1989;2(8659):345-9.

21. National Institute for Health and Clinical Excellence. Clinical Guideline 62 - Antenatal care: routine care for the health pregnant woman. London: National Institute for Health and Clinical Excellence, 2008.

22. Sergent F, Lefevre A, Verspyck E, Marpeau L. Decreased fetal movements in the third trimester: what to do? *Gynecol Obstet Fertil* 2005;33(11):861-9.

23. Froen JF, Heazell AE, Tveit JV, Saastad E, Fretts RC, Flenady V. Fetal movement assessment. *Seminars in perinatology* 2008;32(4):243-6.

24. Saastad E, Vangen S, Froen JF. Suboptimal care in stillbirths - a retrospective audit study. *Acta Obstet Gynecol Scand* 2007;86(4):444-50.

25. Froen JF, Arnestad M, Frey K, Vege A, Saugstad OD, Stray-Pedersen B. Risk factors for sudden intrauterine unexplained death: epidemiologic characteristics of singleton cases in Oslo, Norway, 1986-1995. *Am J Obstet Gynecol* 2001;184(4):694-702.

26. Confidential Enquiry into Stillbirths and Deaths in Infancy. 8th Annual Report, 1 January–31 December 1999. London: Maternal and Child Health Research Consortium, 2001.

27. Manktelow BM, Smith LK, Evans TA, Hyman-Taylor P, Kurinczuk JJ, Field DJ, et al. Perinatal Mortality Surveillance Report - UK Perinatal Deaths for births from January to December 2013. . Leicester:: The Infant Mortality and Morbidity Group, Department of Health Sciences, University of Leicester., 2015.

28. Linde A, Pettersson K, Radestad I. Women's Experiences of Fetal Movements before the Confirmation of Fetal Death--Contractions Misinterpreted as Fetal Movement. *Birth* 2015;42(2):189-94.

29. Preston S, Mahomed K, Chadha Y, Flenady V, Gardener G, MacPhail J, et al. Clinical practice guideline for the management of women who report decreased fetal movements. Brisbane,: Australia and New Zealand Stillbirth Alliance, 2010.

30. Royal College Of Obstetricians and Gynaecologists. Management of Reduced Fetal Movements. London: RCOG, 2011.

31. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al. Reduction of late stillbirth with the introduction of fetal movement information and guidelines - a clinical quality improvement. *BMC pregnancy and childbirth* 2009;9:32.

32. Hofmeyr GJ, Novikova N. Management of reported decreased fetal movements for improving pregnancy outcomes. *Cochrane Database Syst Rev* 2012;4:CD009148.

33. Froen JF, Tveit JV, Saastad E, Bordahl PE, Stray-Pedersen B, Heazell AE, et al. Management of decreased fetal movements. *Seminars in perinatology* 2008;32(4):307-11.

34. Dutton PJ, Warrander LK, Roberts SA, Bernatavicius G, Byrd LM, Gaze D, et al. Predictors of poor perinatal outcome following maternal perception of reduced fetal movements--a prospective cohort study. *PloS one* 2012;7(7):e39784.

35. Royal College Of Obstetricians and Gynaecologists. The Investigation And Management Of The Small-For-Gestational-Age Fetus. London: RCOG, 2013.

36. Heazell AE, Green M, Wright C, Flenady V, Froen JF. Midwives' and obstetricians' knowledge and management of women presenting with decreased fetal movements. *Acta Obstet Gynecol Scand* 2008;87(3):331-9.

37. NHS England. Saving Babies' Lives - A care bundle for reducing stillbirth. Leeds: Acute Care Policy Unit, 2015.

38. Tveit JV, Saastad E, Stray-Pedersen B, Bordahl PE, Flenady V, Fretts R, et al. Correction: Reduction of late stillbirth with the introduction of fetal movement information and guidelines - a clinical quality improvement. *BMC pregnancy and childbirth* 2010;10:49.

39. Winje BA, Wojcieszek AM, Gonzalez-Angulo LY, Teoh Z, Norman J, Froen JF, et al. Interventions to enhance maternal awareness of decreased fetal movement: a systematic review. *Bjog* 2016;123(6):886-98.

40. Mitchell ML. Fetal brain to liver weight ratio as a measure of intrauterine growth retardation: analysis of 182 stillborn autopsies. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc* 2001;14(1):14-9.

41. Barbaux S, Erwich JJ, Favaron PO, Gil S, Gallot D, Golos TG, et al. IFPA meeting 2014 workshop report: Animal models to study pregnancy pathologies; new approaches to study human placental exposure to xenobiotics; biomarkers of pregnancy pathologies; placental genetics and epigenetics; the placenta and stillbirth and fetal growth restriction. *Placenta* 2015;36 Suppl 1:S5-10.

42. Coleman SJ, Gerza L, Jones CJ, Sibley CP, Aplin JD, Heazell AE. Syncytial nuclear aggregates in normal placenta show increased nuclear condensation, but apoptosis and cytoskeletal redistribution are uncommon. *Placenta* 2013;34(5):449-55.

43. Hemming K, Girling A. A menu-driven facility for power and detectable-difference calculations in stepped-wedge cluster-randomized trials. *The Stata Journal* 2014;14:363-80.

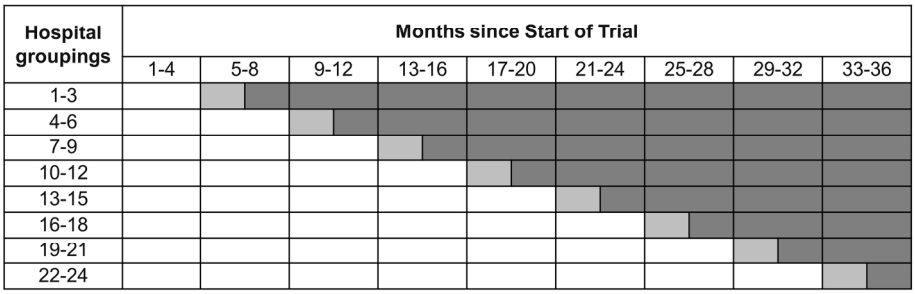
44. Jokhan S, Whitworth MK, Jones F, Saunders A, Heazell AE. Evaluation of the quality of guidelines for the management of reduced fetal movements in UK maternity units. *BMC pregnancy and childbirth* 2015;15:54.

45. Radestad I, Akselsson A, Georgsson S, Lindgren H, Pettersson K, Steineck G. Rationale, study protocol and the cluster randomization process in a controlled trial including 40,000 women investigating the effects of mindfetalness. *Sexual & reproductive healthcare : official journal of the Swedish Association of Midwives* 2016;10:56-61.

FIGURE LEGENDS

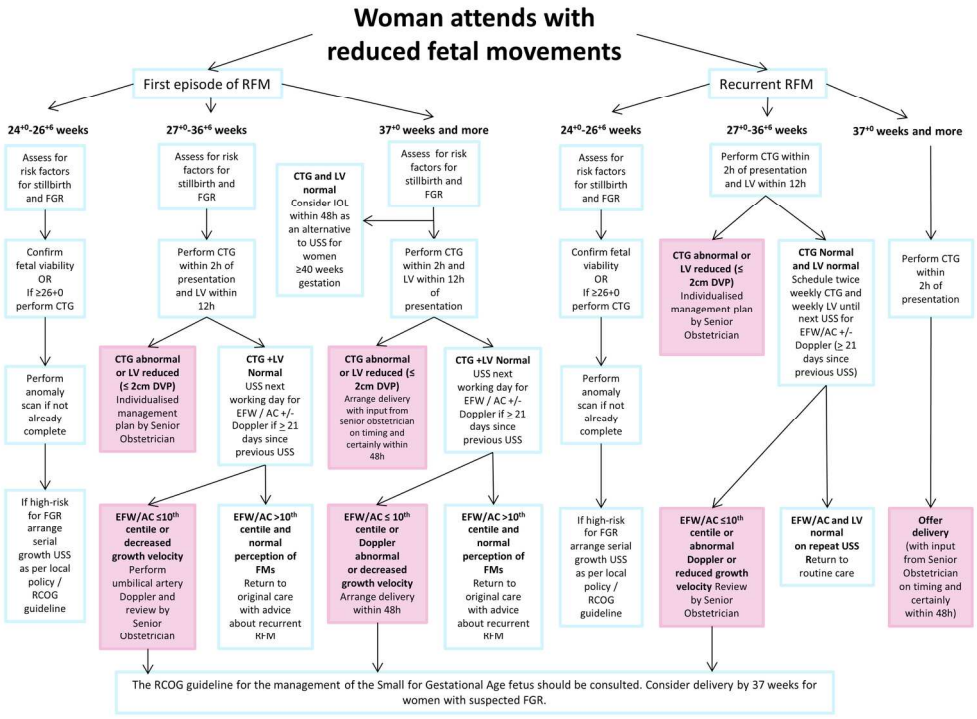
Figure 1 - Stepped wedge design. The shaded areas (both light and dark) indicate periods in which the interventions are being implemented. The lighter areas indicate the “transition” period during which data will not be collected for the control or intervention group. The order in which hospital groupings implement the interventions will be determined via randomization.

Figure 2 – Flow chart for the management of women presenting with reduced fetal movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal movement, USS - ultrasound scan.



Stepped wedge design. The shaded areas (both light and dark) indicate periods in which the interventions are being implemented. The lighter areas indicate the "transition" period during which data will not be collected for the control or intervention group. The order in which hospital groupings implement the interventions will be determined via randomization.

190x142mm (300 x 300 DPI)



Flow chart for the management of women presenting with reduced fetal movements for sites implementing the AFFIRM study. Abbreviations: AC - abdominal circumference, CTG- cardiotocograph, DVP - deepest vertical pool, EFW - estimated fetal weight, FGR - fetal growth restriction, LV - liquor volume, RFM - reduced fetal movement, USS - ultrasound scan.

190x142mm (300 x 300 DPI)

WHO TO CONTACT IF YOU ARE CONCERNED:

(space for sticky with local contact information)

APS Group Scotland
DPPAS33137
Version 3 March 2015

In touch with YOUR BABY

A guide to your baby's movements during pregnancy

AFFIRM

Why are my baby's movements important?

Why are we asking women to get to know their baby's movements?

One of the easiest ways to tell if your baby is healthy is to be aware of how much he or she is moving. Every baby is different and we are asking women to take time to become familiar with their baby's own individual pattern of movements. A reduction or change in **your** baby's movements is what is important.

What can affect my baby's movements?

You are less likely to be aware of your baby's movements when active or busy. Some drugs e.g. strong pain relief or sedatives can get into an unborn baby's circulation and affect the movements. Alcohol and smoking (active and passive smoking) may also affect the baby.

Why are my baby's movements important?

If you notice your baby is moving less than usual, or the pattern of movements has changed, this could be the first sign that your baby may not be well or is not growing properly in the womb. Research has shown that a reduction in the baby's movements may indicate an increased risk of stillbirth. You may hear your midwife or doctor referring to 'reduced fetal movement', or RFM for short.

What are the risks of stillbirth?

Stillbirth affects one in 200 babies after 24 weeks gestation and is one of the most common of the serious complications of pregnancy, affecting the lives of around 4,000 families every year in the UK.

One of the easiest ways to tell if your baby is healthy is to see how much he or she is moving. This booklet tells you what to look out for during your pregnancy.

Every baby is different. It is good to get to know your baby's own movements and the pattern of their sleeping and waking and report to us if you notice a reduction in these movements.

18-24 WEEKS

Most women begin to feel their baby move between 18-24 weeks. At first it may feel like 'bubbles', 'flutterings' or 'like trapped wind'. These are often very short and stop and start. It might take you a little while to be sure what you are feeling. But you will soon get to know the feelings. If this is your second baby, you will know what to look out for and may recognise your baby moving sooner.

Everyone is different when it comes to their movements. There are many reasons you might not feel movements as early as you expect. This includes your body weight, the position of your baby and the location of your placenta. What is important is your baby is growing well. Your midwife will be able to discuss this with you further at your 22 week check.

Try to get to know the times of the day when you are most likely to feel your baby move.

24-36 WEEKS

You will have your own way of describing your baby's own movements. Women often describe their baby's movements as 'rolling', 'kicking', 'pushing', 'jabs', 'elbowing' and 'stretches'.

Between 24-36 weeks you will start to recognise your baby's movements more quickly and become more used to the feeling. It is usually easier to feel your baby's movements when you are lying down, e.g. at night time. It is harder to feel your baby move when you are on your feet and moving around.

Try to get to know the times of the day you are most likely to feel your baby move. This will help you to know if he or she is moving less than normal or if movements have stopped.

Occasionally your baby will get hiccups. These do not count as movements. If you are unsure what you should expect when your baby hiccups, speak to your midwife.

Appendix 2 - Audit of compliance with AFFIRM protocol

Compliance with the AFFIRM management protocol (the management plan for women presenting with reduced fetal movement) will be determined by to means:

A) Telephone / email contact with Principal Investigators at each site to determine which aspects of the AFFIRM protocol have been implemented effectively. This will involve email contact with Principal Investigators to alert them to the request for information, an email detailing the information required, and then a phone call to elicit the information (unless it had already been supplied). Investigators will be asked which of the following elements they had implemented: issuing leaflets to all pregnant women, cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation. "Effective implementation" was defined as the above management for 4/5 of these elements for 80% or more of the time.

B) An audit to determine whether the perception of the site Principal Investigator is supported by review of actual decision making will be performed for the following elements: cardiotocography within 2 hours of presentation, measurement of amniotic fluid volume within 12 hours of presentation, growth scan by the next working day for all women presenting with reduced fetal movement (and who had not had a growth scan within the last three weeks, or who were not being induced within 48 hours), and induction of labour within 48 hours for women presenting with recurrent reduced fetal movement at or after 37 weeks gestation.

This will be conducted by asking sites to complete an audit of the management of all women presenting with reduced fetal movement over the course of one calendar month. Sites will be asked to complete an audit form for each participant. The audit form template (see below) has been generated by the central

AFFIRM study team; anonymized forms will be analysed centrally. There will not be an attempt to corroborate Principal Investigator perception of the proportion of women who were given leaflets, nor will there be any attempt to incorporate the proportion of staff who had completed the e-learning package into analysis of whether any specific site has implemented the intervention or not.

Compliance with AFFIRM reduced fetal movements protocol, One month data collection AUDIT [Month & Year] Unit name: [Name of Hospital]

If you assess a woman with reduced fetal movements (RFM), please complete the questions below. Do not worry if the woman has been seen in other areas of the hospital by other staff, we would rather have multiple reports for the same woman than miss episodes of RFM.

<table>
<tr><td colspan="5">INSERT Patient Sticker (or WRITE name and CHI /NHS number)</td><td colspan="5">AREA WHERE SEEN (CIRCLE)

Triage / Labour ward / Day Assessment Unit (DAU)

Other (specify area i.e. antenatal ward):_____</td></tr>
<tr><td>Date and time of presentation with reduced fetal movements.</td><td colspan="4">DATE: _____/_____/_____

TIME ____:____ am / pm</td><td>GESTATION AND EDD:</td><td colspan="4">_____ WEEKS _____ DAYS

EDD:_____</td></tr>
<tr><td>Referred by (TICK BOX):</td><td>Self</td><td>Community Midwife</td><td>GP</td><td>ANC</td><td>Triage</td><td>DAU</td><td colspan="3">Other (specify:_____ ___</td></tr>
<tr><td>What was the primary reason for attending/phoning? (TICK BOX):</td><td colspan="4">Reduced Fetal Movements</td><td colspan="5">Other (specify: _____</td></tr>
<tr><td>How many times has the woman attended before this visit, with RFM? (TICK BOX):</td><td colspan="2">None – first attendance</td><td colspan="2">Once previously</td><td>Unknown</td><td>Multiple times (please provide the gestation at each presentation i.e. 30+6)</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr>
<tr><td colspan="6">What was the time interval from the woman first being aware of reduced fetal movements and attending the hospital (in hours)?</td><td colspan="5">HOURS: _____</td></tr>
<tr><td>Has she been given a leaflet “Your baby’s movements in pregnancy”?(TICK BOX):</td><td colspan="3">Yes – she already has one</td><td colspan="2">Yes – I have given one to her today</td><td colspan="2">Locally Created Leaflet Given</td><td colspan="3">NO</td></tr>
<tr><td>Has this woman had a growth USS in this pregnancy? (TICK BOX):</td><td colspan="2">No, she has not had a growth scan</td><td colspan="3">Yes, within the last 3 weeks (date of scan):

DATE: _____/_____/_____</td><td colspan="4">Yes, but more than 3 weeks ago (date of scan):

DATE: _____/_____/_____</td></tr>
</table>

CONTINUATION: NHS/ CHI NUMBER: ……

Are any of the following risk factors for Fetal growth restriction present (CIRCLE all that apply)?							
Age ≥40 or ≤16	Smoker ≥20cpd	Known or suspected growth restriction	Congenital anomaly	Raised BP (essential hypertension, pre-eclampsia or pregnancy induced hypertension)	Previous pre-eclampsia	Diabetes or gestational diabetes	Previous FGR or stillbirth

What investigations were conducted during this episode of reduced fetal movement?			
Please record below the date and time that these investigations were completed or indicate if not performed.			**Please provide the results (CIRCLE):**
CTG	Not performed ☐	DATE: ___/___/_____ TIME: _____:_____ am/pm *Computerised CTG*: YES / NO (CIRCLE)	Normal / Suspicious / Pathological
Liquor volume assessment on scan	Not performed ☐	DATE: ___/___/_____ TIME: _____:_____ am/pm	Normal / Reduced / Increased
Growth scan	Not performed ☐	DATE: ___/___/_____ TIME: _____:_____ am/pm	Normal / EFW < 10th centile/ AC < 10th centile / EFW and AC < 10th centile
Umbilical Artery Doppler	Not performed ☐	DATE: ___/___/_____ TIME: _____:_____ am/pm	Normal/.> 95th centile/absent EDF/reversed EDF
MCA Doppler	Not performed ☐	DATE: ___/___/_____ TIME: _____:_____ am/pm	Normal/<5th centile

DELIVERY METHOD (If available)			
Was the woman offered induction of labour	YES / NO (CIRCLE) **IF Yes,** please provide date, time and method of the induction:	DATE: _____/ _____/ _____ TIME: _____:_____ am/pm	
Was the woman offered elective caesarean section as a result of the reduced fetal movement?	YES / NO (CIRCLE) **IF Yes,** please provide date, time and reason:	DATE: _____/ _____/ _____ TIME: _____:_____ am/pm	Please provide the reason for the elective Caesarean section:

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____Page 1____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____Page 4____
	2b	All items from the World Health Organization Trial Registration Data Set	_Included throughout protocol_
Protocol version	3	Date and version identifier	_____Page 4 ____
Funding	4	Sources and types of financial, material, and other support	___Pages 31-32__
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_Names and affiliations Page 1 and 2; Contributions Page 32_
	5b	Name and contact information for the trial sponsor	____Page 27___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_Not applicable__

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____Page 27___
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__Pages 5-12___
	6b	Explanation for choice of comparators	__Pages 8-10____
Objectives	7	Specific objectives or hypotheses	__Page 12__
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	__Pages 15-16 and Figure 1 ____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__Pages 15 & 24_
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__Pages 16-17___
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__Pages 19-20 and Figure 2___
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	__Not applicable in AFFIRM trial__
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__Pages 19-20___
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__Not applicable_

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__Pages 13-14___
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Randomisation by site explained in Figure 1 and Pages 18-19___
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__Pages 23-25 __
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__Page 23 _____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__Pages 18-19___
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__Page 19 _____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__Page 19 ____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__Page 19 ____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_ Not applicable in AFFIRM study___

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__Pages 20-23___
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__Not applicable_
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__Pages 21-22__
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__Pages 25-26___
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__Pages 25-26___
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__Pages 25-26__

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_DMC not required, explanation Pg 27___
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__Pages 20, 28-29__
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__Pages 26-27__
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	__Page 15_____

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___Page 28_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	___Page 28_____
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___Page 28_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__Not applicable_
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__Pages 21-22___
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__Page 32_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__Page 30_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__Page 27_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__Page 30____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__Page 31 ____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Not applicable_

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_Not Applicable__
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_Not Applicable__

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.